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(21) International Application Number: PCT/US96/12917 (22) International Filing Date: 8 August 1996 (08.08.96) (30) Priority Data: <table border="0" style="width: 100%;"><tr><td style="width: 30%;">60/002,093</td><td style="width: 40%;">10 August 1995 (10.08.95)</td><td style="width: 30%;">US</td></tr><tr><td>60/014,181</td><td>26 March 1996 (26.03.96)</td><td>US</td></tr><tr><td>9607254.1</td><td>4 April 1996 (04.04.96)</td><td>GB</td></tr><tr><td>9609264.8</td><td>2 May 1996 (02.05.96)</td><td>GB</td></tr></table> (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DE LASZLO, Stephen, E. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MANTLO, Nathan, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PONTICELLO, Gerald, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SELNICK, Harold, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). LIVERTON, Nigel, J. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	60/002,093	10 August 1995 (10.08.95)	US	60/014,181	26 March 1996 (26.03.96)	US	9607254.1	4 April 1996 (04.04.96)	GB	9609264.8	2 May 1996 (02.05.96)	GB	(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
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(54) Title: 2-SUBSTITUTED ARYL PYRROLES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE (57) Abstract <p>The present invention addresses 2-substituted aryl pyrroles, as well as compositions containing such compounds and methods of treatment. Cytokine mediated diseases refers to diseases or conditions in which excessive or unregulated production or activity of one or more cytokines occurs. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF) are cytokines which are involved.</p>													

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TITLE OF THE INVENTION

2-SUBSTITUTED ARYL PYRROLES, COMPOSITIONS
CONTAINING SUCH COMPOUNDS AND METHODS OF USE

5 CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application based upon U. S. Application No. 60/002,093 filed on August 10, 1995 and U. S. Application No. 60/014,181 filed on March 26, 1996, priority of which is claimed hereunder.

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BACKGROUND OF THE INVENTION

The present invention addresses 2-substituted aryl pyrroles, as well as compositions containing such compounds and methods of treatment.

15

Cytokine mediated diseases refers to diseases or conditions in which excessive or unregulated production of one or more cytokines occurs. Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are cytokines produced by a variety of cells, which are involved in immunoregulation and other physiological conditions, such as inflammation.

20

IL-1 has been demonstrated to mediate a variety of biological activities. [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T-helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

25

There are many disease states in which IL-1 is implicated. Included among these diseases are rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, other acute or chronic inflammatory diseases, such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute

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synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating rheumatoid arthritis, 5 rheumatoid spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft 10 v. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

15 Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)]. Therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells. TNF has also been implicated in various roles 20 with other viral infections, such as the cytomegalo virus (CMV), influenza virus and the herpes virus.

IL-6 is a cytokine effecting the immune system, hematopoiesis and acute phase reactions. It is produced by several mammalian cell types in response to agents such as IL-1 and is 25 correlated with disease states such as angiofollicular lymphoid hyperplasia.

Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), 30 monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Like IL-1, IL-8 is produced by several cell types, including mononuclear cells, fibroblasts, and endothelial cells. Its production is induced by IL-1, TNF and by lipopolysaccharide (LPS). IL-8 stimulates

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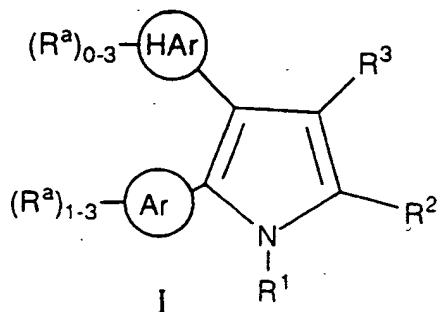
a number of cellular functions in vitro. It is a chemoattractant for neutrophils, T-lymphocytes and basophils. It induces histamine release from basophils. It causes lysosomal enzyme release and respiratory burst from neutrophils, and it has been shown to increase the surface expression of Mac-1 (CD11b/CD 18) on neutrophils without de novo protein synthesis. There remains a need for treatment, in this field, for compounds which are cytokine suppressive or antagonistic, i.e., compounds which are capable of interfering with, inhibiting or antagonizing cytokines such as IL-1, IL-6, IL-8 and TNF.

The compounds of formula I are also useful in treating diseases characterized by excessive IL-8 activity. There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis.

The compounds in the present invention are used for the treatment of cytokine mediated diseases.

SUMMARY OF THE INVENTION

The present invention is directed to a compound represented by formula I:



or a pharmaceutically acceptable salt thereof, wherein:

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(Ar) represents a C₅₋₁₀ aryl or heteroaryl group, said aryl or heteroaryl group being substituted with 1 - 3 groups selected from R^a;

(HAr) represents a heteroaryl group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 - 3 R^a groups;

each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²⁰, CO₂R²³; CONR²⁰R²³; SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰ C(NR²⁰)NR²⁰R²³; CONR²⁰SO₂R²¹ and SO₂NR²⁰CO₂R²¹;

R¹ is selected from the group consisting of: H; C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, aryl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, and C(O)OCH₂OC(O)R²⁰;

R² is selected from the group consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, and C₂₋₁₅ alkynyl, heterocyclyl, said alkyl, alkenyl and alkynyl optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or NR²⁴; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³,

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SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³,
 NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰,
 CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹,
 OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

5

R³ is selected from the group consisting of: H, C₁₋₁₅ alkyl,
 C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, CF₃, OCF₃, NO₂, heterocyclyl, CN,
 S(O)R²¹, SO₂R²¹, COR²⁰, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
 SO₂NR²⁰CONR²⁰R²³, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹ and
 10 SO₂NR²⁰CO₂R²¹; said alkyl, alkenyl, alkynyl and heterocyclyl being
 optionally substituted with from one to three members selected from the
 group consisting of: halo, CN, aryl, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³,
 S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
 SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³,
 15 NR²⁰C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹,
 NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²¹ and OCONR²⁰R²³;

R²⁰ represents a member selected from the group
 consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl,
 20 aryl and heteroaryl, said alkyl, alkenyl, aryl, heteroaryl, heterocyclyl
 and alkynyl being optionally substituted with 1-3 groups selected from
 halo, aryl and heteroaryl;

R²¹ represents a member selected from the group
 25 consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl,
 aryl and heteroaryl, said alkyl, alkenyl and alkynyl optionally
 interrupted by oxo and/or 1-2 heteroatoms selected from O, S, S(O),
 SO₂ or NR²⁴; said alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and
 heteroaryl being optionally substituted with from 1-3 of halo,
 30 heterocyclyl, aryl, heteroaryl, CN, OR²⁰, O((CH₂)_nO)_mR²⁰,
 NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 2 to 4,
 and m represents an integer of from 1 to 3: SR²⁰, NR²⁰R²³, S(O)R²²,
 SO₂R²², SO₂NR²⁰R²³, SO₂NR²⁰COR²², SO₂NR²⁰CONR²⁰R²³,
 NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CONR²⁰R²³, NR²²C(NR²²)NHR²².

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CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²², NR²⁰SO₂R²²,
SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², and OCONR²⁰R²³;

R²² is selected from the group consisting of: C₁₋₁₅ alkyl,
5 C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said
alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo,
aryl or heteroaryl groups;

R²³ is R²¹ or H;
10

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂,
R²³ and SO₂R²²;

and when two R²⁰ groups are present, when R²⁰ and R²¹
15 are present, or when R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰
and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms
to which they are attached and any intervening atoms and represent
heterocyclyl containing from 5-10 atoms, at least one atom of which is a
heteroatom selected from O, S or N, said heterocyclyl optionally
20 containing 1-3 additional N atoms and 0-1 additional O or S atom.

Also included in the invention is a pharmaceutical
composition which is comprised of a compound of formula I in
combination with a pharmaceutically acceptable carrier.

Also include in the invention is a method of treating a
25 cytokine mediated disease in a mammal, comprising administering to a
mammalian patient in need of such treatment an amount of a compound
of formula I which is effective to treat said cytokine mediated disease.

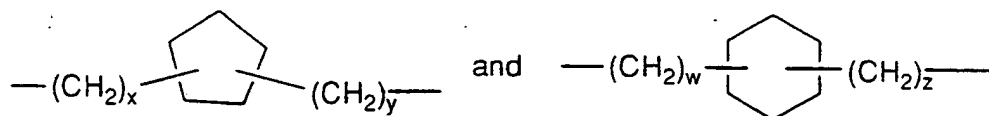
Also included in the invention is a method of treating
diabetes in a mammalian patient in need of such treatment, comprising
30 administering to said patient an anti-diabetic effective amount of a
compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion. Examples include the following:



wherein: x plus y = from 0-10; and w plus z = from 0-9.

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups.

The group Ar represents a 5-10 membered aryl or heteroaryl which is substituted with 1 - 3 groups selected from R^a such that a total of 1 to 4 groups are attached to Ar . Preferred Ar are phenyl and naphthyl.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type

are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine and pyrazine and triazine.

The group HAr thus represents a heteroaryl group which contains from 5 to 10 atoms. One to three atoms are heteroatoms which are selected from O, S and N. In addition, there may be up to three additional nitrogen atoms, and 0-1 additional O or S. The heteroaryl group may be unsubstituted or substituted with up to 3 R^a groups. HAr is carbon linked except where it is a purinyl, imidazolyl or imidazopyridine in which case it may be attached at the nitrogen or carbon atom.

Preferred heteroaryl groups represented by HAr are as follows: pyridyl, quinolyl, purinyl, imidazolyl, imidazopyridyl and pyrimidinyl.

The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S, SO, SO₂ or N, and in which up to three additional carbon atoms may be optionally replaced by heteroatoms.

Heterocyclyl is carbon or nitrogen linked; if carbon linked and contains a nitrogen, then the nitrogen may be substituted by R^{24} . Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazo[4.5-c]pyridinyl, imidazolyl, piperazinyl, pyrrolidine-2-onyl, piperidin-2-onyl and the like.

The term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

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The term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor-beta (TNF- β).

By the term "cytokine antagonizing, interfering or cytokine suppressive amount" is meant an amount of a compound of formula I which will, cause a decrease in the *in vivo* activity level of the cytokine to normal or sub-normal levels, when given to the patient for the prophylaxis or therapeutic treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production or activity.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

Throughout the instant application, the following abbreviations are used with the following meanings:

	Bu	butyl
	Bn	benzyl
	BOC, Boc	t-butyloxycarbonyl
25	calc.	calculated
	CBZ, Cbz	Benzyloxycarbonyl
	CDI	N,N'-carbonyl diimidazole
	FAB-MS	Fast atom bombardment-mass spectroscopy
	HPLC	High pressure liquid chromatography
30	KHMDS	Potassium bis(trimethylsilyl)amide
	LAH	Lithium aluminum hydride
	LHMDS	Lithium bis(trimethylsilyl)amide
	Me	methyl
	MeOH	methanol

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	MPLC	Medium pressure liquid chromatography
	NMR	Nuclear Magnetic Resonance
	Ph	phenyl
	Pr	propyl
5	prep.	prepared
	Pyr.	pyridyl
	TMS	Trimethylsilyl

One subset of compounds of the invention relates to

10 compounds of formula I wherein Ar represents a member selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, thiophenyl, furanyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl and isoxazolyl. Within this subset, all other variables are as originally defined.

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Another subset of compounds of the invention relates to compounds of formula I wherein R^a is selected from the group consisting of: halo, CN, R^{21} , OR^{23} , CO_2R^{23} and $CONR^{20}R^{23}$. Within this subset, all other variables are as originally defined.

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Another subset of compounds of the invention relates to

compounds of formula I wherein HAr represents a member selected from the group consisting of: pyridyl, quinolyl, purinyl, imidazolyl, pyrimidinyl and imidazopyridyl. Within this subset, all other variables are as originally defined.

25

Another subset of compounds of the invention relates to compounds of formula I wherein R^1 is a member selected from the group consisting of: H, C₁₋₁₅ alkyl and C₁₋₁₅ alkyl substituted as originally defined. Within this subset, all other variables are as originally defined.

30

Another subset of compounds of the invention relates to compounds of formula I wherein R^2 represents a member selected from one of the following groups:

- a) -C₁₋₇-straight or branched alkyl optionally interrupted by oxo or NR^{24} and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$, $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{23}$ and $OCONR^{20}R^{21}$;
- b) -C₄₋₇-cycloalkyl optionally interrupted by oxo or NR^{24} and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$, $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{23}$ and $OCONR^{20}R^{21}$;
- c) -C₁₋₄-alkyl-aminoacyl-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} , and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$, $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{23}$ and $OCONR^{20}R^{21}$;
- d) -C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} , and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$, $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{23}$ and $OCONR^{20}R^{21}$;

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- e) -C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹; and
- f) -C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹.
- The point of attachment to the pyrrole is from the left hand side of the items listed in a through f. Within this subset, all other variables are as originally defined.

Another subset of compounds of the invention relates to compounds of formula I wherein R³ represents a member selected from the group consisting of:

- a) H,
 b) alkyl,
 c) halo,
 d) CO₂R²⁰,
 e) CONR²⁰R²³ and
 f) CN.

Within this subset, all other variables are as originally defined.

A preferred subset of compounds of the invention relates to compounds of formula I wherein:

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Ar

is selected from the group consisting of:

- 5
- a) phenyl,
 - b) pyridyl,
 - c) pyrimidinyl,
 - d) thiophenyl,
 - e) furanyl,
 - f) imidazolyl,
 - g) thiazolyl,
 - 10 h) isothiazolyl,
 - i) oxazolyl, and
 - j) isoxazolyl;

15 R^a represents a member selected from the group consisting of: halo, CN, R^{21} , OR^{23} , CO_2R^{23} and $CONR^{20}R^{23}$;

HAr

is selected from the group consisting of:

- 20
- a) pyridyl,
 - b) quinolyl,
 - c) purinyl,
 - d) imidazolyl,
 - e) pyrimidinyl and
 - f) imidazopyridine;

25 R^1 is:

- a) H or
- b) C_{1-15} alkyl unsubstituted or substituted with 1-3 groups selected from the group consisting of: aryl, heteroaryl, OR^{20} , SR^{20} , $N(R^{20})_2$, $S(O)R^{21}$, SO_2R^{21} , $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{21}$,
30 $SO_2NR^{20}CONR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$,

- 15 -

$\text{NR}^{20}\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$ and $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$;

R^2 is selected from the group consisting of:

- 5 a) -C₁₋₇-straight or branched alkyl optionally interrupted by oxo or NR^{24} , and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $\text{NR}^{20}\text{R}^{23}$, $\text{S}(\text{O})\text{R}^{23}$, SO_2R^{23} , $\text{SO}_2\text{NR}^{20}\text{R}^{23}$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{21}$, $\text{NR}^{20}\text{COR}^{23}$, $\text{NR}^{20}\text{CO}_2\text{R}^{23}$,
 10 $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$, $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{20}$, CO_2R^{20} , $\text{CONR}^{20}\text{R}^{23}$, $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{NR}^{20}\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{23}$ and $\text{OCONR}^{20}\text{R}^{21}$;
- b) -C₄₋₇-cycloalkyl optionally interrupted by oxo or NR^{24} , and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} ,
 15 $\text{NR}^{20}\text{R}^{23}$, $\text{S}(\text{O})\text{R}^{23}$, SO_2R^{23} , $\text{SO}_2\text{NR}^{20}\text{R}^{23}$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{21}$, $\text{NR}^{20}\text{COR}^{23}$, $\text{NR}^{20}\text{CO}_2\text{R}^{23}$, $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$, $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{20}$, CO_2R^{20} , $\text{CONR}^{20}\text{R}^{23}$, $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{NR}^{20}\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{23}$ and $\text{OCONR}^{20}\text{R}^{21}$;
- 20 c) -C₁₋₄-alkyl-aminoacyl-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} , and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $\text{NR}^{20}\text{R}^{23}$, $\text{S}(\text{O})\text{R}^{23}$,

 25 SO_2R^{23} , $\text{SO}_2\text{NR}^{20}\text{R}^{23}$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{21}$, $\text{NR}^{20}\text{COR}^{23}$, $\text{NR}^{20}\text{CO}_2\text{R}^{23}$, $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$, $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{20}$, CO_2R^{20} , $\text{CONR}^{20}\text{R}^{23}$, $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{NR}^{20}\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{23}$ and $\text{OCONR}^{20}\text{R}^{21}$;
- d) -C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} , and
 30 optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $\text{NR}^{20}\text{R}^{23}$, $\text{S}(\text{O})\text{R}^{23}$, SO_2R^{23} , $\text{SO}_2\text{NR}^{20}\text{R}^{23}$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{21}$, $\text{NR}^{20}\text{COR}^{23}$, $\text{NR}^{20}\text{CO}_2\text{R}^{23}$, $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$,

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$N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$,
 $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $CONR^{20}SO_2R^{23}$ and $CONR^{20}R^{21}$;

e) -C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl, the alkyl
portions thereof being optionally interrupted by oxo or NR^{24} , and
5 optionally substituted by 1-3 groups selected from the group consisting
of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$,
 $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$,
 $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$,
 $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$,
10 $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $CONR^{20}SO_2R^{23}$ and $CONR^{20}R^{21}$.
and

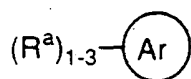
f) -C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl, the
alkyl portions thereof being optionally interrupted by oxo or NR^{24} , and
optionally substituted by 1-3 groups selected from the group consisting
15 of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$,
 $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$,
 $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$,
 $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$,
 $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $CONR^{20}SO_2R^{23}$ and $CONR^{20}R^{21}$.

20

R^3 is selected from the group consisting of:

- a) H,
b) alkyl,
c) halo,
25 d) CO_2R^{20} ,
e) $CONR^{20}R^{23}$ and
f) CN.

A subset of the most preferred compounds of formula I is
30 realized when:

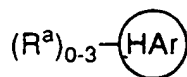


is selected from the group consisting of:

- a) 4-fluorophenyl.

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- | | | |
|----|-----|-------------------------------------|
| | b) | 4-chlorophenyl, |
| | c) | 3-fluorophenyl, |
| | d) | 3-chlorophenyl, |
| 5 | e) | 4-fluorothiophen-2-yl, |
| | f) | 4-fluorothiophen-3-yl, |
| | g) | 5-fluorothiophen-2-yl, |
| | h) | 5-fluorothiophen-3-yl, |
| | i) | 4-chlorothiophen-2-yl, |
| | j) | 4-chlorothiophen-3-yl, |
| 10 | k) | 5-chlorothiophen-2-yl, |
| | l) | 5-chlorothiophen-3-yl, |
| | m) | 3-methylphenyl, |
| | n) | 3,4-dichlorophenyl, |
| | o) | 3-hydroxyphenyl, |
| 15 | p) | 2-chlorophenyl, |
| | q) | 4-aminomethylphenyl, |
| | r) | 4-nitrophenyl, |
| | s) | 3,4-difluorophenyl, |
| | t) | 2-methoxyphenyl, |
| 20 | u) | 3-methoxyphenyl, |
| | v) | 4-methoxyphenyl, |
| | w) | 4-(4-(N-acetyl)-piperazinyl-phenyl, |
| | x) | 4-morpholinyl-phenyl, |
| | y) | 3-trifluoromethylphenyl, |
| 25 | z) | 4-methylsulfinylphenyl, and |
| | aa) | 4-methylsulfonylphenyl; |



is selected from the group consisting of:

- | | | |
|----|----|-----------------------|
| 30 | a) | 4-pyridyl, |
| | b) | 4-(2-methylpyridyl), |
| | c) | 4-(2-aminopyridyl), |
| | d) | 4-(2-methoxypyridyl), |
| | e) | 4-quinolinyl, |

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- 5 f) 4-pyrimidinyl,
 g) 9-purinyl,
 h) 7-(imidazo[4,5-b]pyridyl),
 i) 4-(3-methylpyridyl),
 j) 2-pyrimidinyl,
 k) 3-pyridazinyl.
 l) 2-pyrazinyl,
 m) 2-(N-t-butoxycarbonylamino)-4-pyridyl,
 n) 4-(2-N-acetylamino)-pyridyl,
10 o) 4-(2-N-benzoylamino-3-methyl)-pyridyl and
 p) 4-(2-N-benzoylamino)-pyridyl;

R¹ is: H:

15 R² is selected from the group consisting of:

- a) isopropyl,
 b) tert-butyl,
 c) phenethyl,
 d) benzyl,
20 e) 2-amino-2,2-dimethylethyl,
 f) 4-aminomethylbenzyl,
 g) piperidin-4-yl,
 h) piperidin-3-yl,
 i) pyrrolidin-3-yl,
25 j) N-methylpiperidin-4-yl,
 k) N-benzylpiperidin-4-yl,
 l) N-(2-hydroxyethyl)piperidin-4-yl,
 m) N-methanesulfonylpiperidin-4-yl,
 n) isobutyl,
30 o) N-(benzyloxycarbonyl)-piperidin-4-yl,
 p) N-morpholinylmethyl
 q) N-(phenyl)-piperidin-4-yl.
 r) N-(methyl)-piperidin-4-yl-methyl,
 s) N-methyl-piperidin-3-yl.

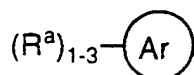
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and

R³ is selected from the group consisting of:

- 5 a) H,
 b) F,
 c) Cl,
 d) Br,
 d) CO₂R²⁰,
10 e) CONR²⁰R²³ and
 f) CN.

Another subset of the most preferred compounds of formula I is realized when:

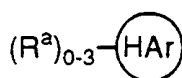


is selected from the group consisting of:

- 15 a) 4-fluorophenyl,
 b) 4-chlorophenyl,
 c) 3-fluorophenyl,
 d) 3-chlorophenyl,
 e) 4-fluorothiophen-2-yl,
 f) 4-fluorothiophen-3-yl,
20 g) 5-fluorothiophen-2-yl,
 h) 5-fluorothiophen-3-yl,
 i) 4-chlorothiophen-2-yl,
 j) 4-chlorothiophen-3-yl,
 k) 5-chlorothiophen-2-yl,
25 l) 5-chlorothiophen-3-yl,
 m) 3-methylphenyl,
 n) 3,4-dichlorophenyl,
 o) 3-hydroxyphenyl,
 p) 2-chlorophenyl,
30 q) 4-aminomethylphenyl,
 r) 4-nitrophenyl,
 s) 3,4-difluorophenyl,
 t) 2-methoxyphenyl,
 u) 3-methoxyphenyl.

- 20 -

- 5
- v) 4-methoxyphenyl,
 - w) 4-(4-(N-acetyl)-piperazinyl-phenyl,
 - x) 4-morpholinyl-phenyl,
 - y) 3-trifluoromethylphenyl,
 - z) 4-methylsulfinylphenyl, and
 - aa) 4-methylsulfonylphenyl;



is selected from the group consisting of:

- 10
- a) 4-pyridyl,
 - b) 4-(2-methylpyridyl),
 - c) 4-(2-aminopyridyl),
 - d) 4-(2-methoxypyridyl),
 - e) 4-quinolinyl,
 - f) 4-pyrimidinyl,
 - 15 g) 9-purinyl,
 - h) 7-(imidazo[4.5-b]pyridyl),
 - i) 4-(3-methylpyridyl),
 - j) 2-pyrimidinyl,
 - k) 3-pyridazinyl,
 - 20 l) 2-pyrazinyl,
 - m) 2-(N-t-butoxycarbonylamino)-4-pyridyl,
 - n) 4-(2-N-acetylamino)-pyridyl,
 - o) 4-(2-N-benzoylamino-3-methyl)-pyridyl and
 - p) 4-(2-N-benzoylamino)-pyridyl;

25

R¹ is: C₁₋₁₅ alkyl;

R² is selected from the group consisting of:

- 30
- a) isopropyl,
 - b) tert-butyl,
 - c) phenethyl,
 - d) benzyl,
 - e) 2-amino-2,2-dimethylethyl.

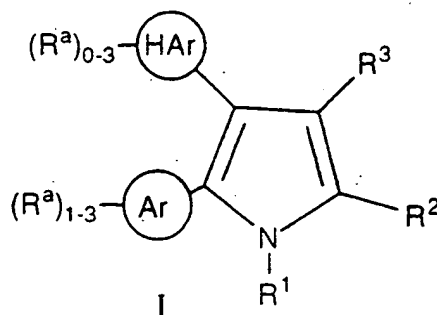
- 21 -

- 5
- 10
- 15
- f) 4-aminomethylbenzyl,
 - g) piperidin-4-yl,
 - h) piperidin-3-yl,
 - i) pyrrolidin-3-yl,
 - j) N-methylpiperidin-4-yl,
 - k) N-benzylpiperidin-4-yl,
 - l) N-(2-hydroxyethyl)piperidin-4-yl,
 - m) N-methanesulfonylpiperidin-4-yl,
 - n) isobutyl,
 - o) N-(benzyloxycarbonyl)-piperidin-4-yl,
 - p) N-morpholinylmethyl
 - q) N-(phenyl)-piperidin-4-yl,
 - r) N-(methyl)-piperidin-4-yl-methyl,
 - s) N-methyl-piperidin-3-yl,
- and

R^3 is selected from the group consisting of:

- 20
- 25
- a) H,
 - b) F,
 - c) Cl,
 - d) Br,
 - d) CO_2R^{20} ,
 - e) $\text{CONR}^{20}R^{23}$ and
 - f) CN.

A further subset of compounds of the invention relates to a compound represented by formula I:



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or a pharmaceutically acceptable salt thereof, wherein:



represents a C₅₋₁₀ aryl or heteroaryl group, substituted with 1 - 3 groups selected from R^a;

5



represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 - 3 R^a groups;

10

each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²⁰, CO₂R²³; CONR²⁰R²³; SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; SO₂NR²⁰CO₂R²¹; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰ and C(NR²⁰)NR²⁰R²³;

15

R¹ is selected from the group consisting of: H; C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, aryl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CON(R²⁰)₂, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCON(R²⁰)₂, OCONR²⁰SO₂R²¹, C(O)OCH₂OC(O)R²⁰ and OCONR²⁰R²³;

25

R² is selected from the group consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, and C₂₋₁₅ alkynyl, heterocyclyl, optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from

30

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1-3 of halo, aryl, heteroaryl, OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} ,
 $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{COR}^{22}$,
 $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{N}(\text{R}^{22})\text{C}(\text{NR}^{22})\text{NHR}^{22}$, CO_2R^{20} ,
 $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$,
5 $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$ and $\text{OCONR}^{20}\text{R}^{23}$;

R^3 is selected from the group consisting of: H, C_{1-15} alkyl,
 C_{2-15} alkenyl, C_{2-15} alkynyl, halo, CF_3 , NO_2 and heterocyclyl, said
alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with
10 from one to three members selected from the group consisting of: halo,
CN, aryl, heteroaryl, OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} ,
 $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{COR}^{22}$,
 $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$, CO_2R^{20} ,
 $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$,
15 $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$ and $\text{OCONR}^{20}\text{R}^{23}$;

R^{20} represents a member selected from the group
consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl,
aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally
20 substituted with 1-3 groups selected from halo, aryl and heteroaryl;

R^{21} represents a member selected from the group
consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, aryl and
heteroaryl, optionally interrupted by 1-2 heteroatoms selected from O,
25 S, $\text{S}(\text{O})$, SO_2 or NR^{24} ; said alkyl, alkenyl, alkynyl, aryl and heteroaryl
being optionally substituted with from 1-3 of halo, heterocyclyl, aryl,
heteroaryl, CN, OR^{20} , $\text{O}((\text{CH}_2)_n\text{O})_m\text{R}^{20}$, $\text{NR}^{20}((\text{CH}_2)_n\text{O})_m\text{R}^{20}$ wherein
n represents an integer of from 2 to 4, and m represents an integer of
from 1 to 3: SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$,
30 $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$,
 $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$, CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$,
 $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$,
 $\text{OCONHR}^{20}\text{R}^{23}$ and $\text{OCON}(\text{R}^{20})_2$;

- 24 -

R²² is selected from the group consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

5

R²³ is R²¹ or H;

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂, R²³ and SO₂R²²;

10

n is 1-4;

m is 1-4;

15

and when two R²⁰ groups are present, when R²⁰ and R²¹ are present, or when R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

20

Another subset of the compounds of the invention relates to compounds of formula I wherein:

25



is selected from the group consisting of:

30

- a) phenyl,
- b) pyridyl,
- c) pyrimidinyl,
- d) thiophenyl,
- e) furanyl,
- f) imidazolyl,
- g) thiazolyl.

- 25 -

- h) isothiazolyl,
- i) oxazolyl and
- j) isoxazolyl;

(HAr)

5 is selected from the group consisting of:

- a) pyridyl,
- b) quinolyl,
- c) purinyl,
- d) imidazolyl and
- 10 e) imidazopyridyl;

R¹ is:

- a) H or
 - b) substituted alkyl;
- 15

R² is selected from the group consisting of:

- a) -C₁-7-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo or NR²³,
- b) -C₄-7-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo or NR²³,
- 20 c) -C₁-4-alkyl-aminoacyl-C₂-6-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo or NR²³,
- d) -C₁-4-alkyl-aminoacyl-C₄-7-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³ or NR²⁴.
- 25 e) -C₁-4-alkyl-aminoacylamino-C₂-6-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³ or
- f) -C₁-4-alkyl-aminoacylamino-C₄-7-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³ or NR²⁴; wherein the point of attachment to the pyrrole is
- 30 from the left hand side of the items listed in a through f; and

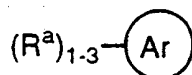
R³ is:

- a) H,
- b) alkyl.

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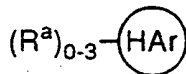
- c) halo, or
- d) CO_2R^{20} .

Still another subset of compounds of the invention relates to
 5 compounds of formula I of subset A wherein:



is selected from the group consisting of:

- a) phenyl,
- b) 4-fluorophenyl,
- 10 c) 4-chlorophenyl,
- d) 3-fluorophenyl,
- e) 3-chlorophenyl,
- f) thiophen-2-yl,
- 15 g) thiophen-3-yl,
- h) 4-fluorothiophen-2-yl,
- i) 4-fluorothiophen-3-yl,
- j) 5-fluorothiophen-2-yl,
- k) 5-fluorothiophen-3-yl,
- 20 l) 4-chlorothiophen-2-yl,
- m) 4-chlorothiophen-3-yl,
- n) 5-chlorothiophen-2-yl,
- o) 5-chlorothiophen-3-yl,
- p) 3-methylphenyl,
- q) 3,4-dichlorophenyl, and
- 25 r) 3-hydroxyphenyl:



is selected from the group consisting of:

- a) 4-pyridyl,
- b) 4-(2-methylpyridyl),
- 30 c) 4-(2-aminopyridyl),
- d) 4-(2-methoxypyridyl),
- e) 4-quinolyl,

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- f) 4-pyrimidinyl,
- g) 9-purinyl,
- h) 7-(imidazo[4,5-b]pyridinyl), and
- i) 4-(3-methylpyridyl);

5

R¹ is: H;

R² is selected from the group consisting of:

- a) isopropyl,
- 10 b) tert-butyl,
- c) phenethyl,
- d) benzyl,
- e) 2-amino-2,2-dimethylethyl,
- f) 4-aminomethylbenzyl,
- 15 g) glycylaminomethyl,
- h) (L)-alanylaminomethyl,
- i) 2-amino-2,2-dimethylacetylaminomethyl,
- j) N,N-dimethylaminoethyl-N-methylaminocarbonylaminomethyl,
- 20 k) 3-piperidinecarbonylaminomethyl,
- l) 4-piperidinecarbonylaminomethyl,
- m) piperidin-4-yl,
- n) piperidin-3-yl,
- o) pyrrolidin-3-yl,
- 25 p) N-methylpiperidin-4-yl,
- q) N-benzylpiperidin-4-yl,
- r) N-(2-hydroxyethyl)piperidin-4-yl and
- s) N-methanesulfonylpiperidin-4-yl; and

30 R³ is selected from the group consisting of:

- a) H,
- b) F,
- c) Cl and
- d) Br.

The pharmaceutically acceptable salts of the compounds of formula I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of formula I formed e.g. from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention.

This invention also relates to a method of antagonizing or inhibiting the production or activity of cytokines in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula I to antagonize or inhibit cytokine production or activity such that it is regulated down to normal levels, or in some cases to subnormal levels, so as to ameliorate or prevent the disease state.

The compounds of formula I can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of disease states in mammals, which are exacerbated or caused by excessive or unregulated cytokines production, more specifically IL-

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1, IL-6, IL-8 or TNF, by such mammal's cells, such as but not limited to monocytes and/or macrophages.

Compounds of formula I inhibit cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore useful for treating inflammatory diseases, such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

The compounds of formula I may be used to treat other disease states mediated by excessive or unregulated cytokine production or activity. Such diseases include, but are not limited to sepsis, e.g., gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejection, fever and myalgia due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS and other viral infections, ARC (AIDs related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, such as cytomegalovirus (CMV), influenza virus and the herpes family of viruses such, as Herpes Zoster or Simplex I and II.

The compounds of formula I may also be used topically in the treatment of inflammation such as for the treatment of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The compounds of formula I are normally formulated as pharmaceutical compositions, which are comprised of a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I may also be administered in combination with a second therapeutically active compound. These procedures may involve

- 30 -

mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, solid or liquid. Solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Liquid carriers include syrup, peanut oil, olive oil, water and the like. Similarly, the carrier may include time delay material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid dosage form is used, the preparations typically be in the form of a tablet, hard gelatin capsule, a troche or lozenge. The amount of solid will vary widely but preferably will be from about 0.025 mg to about 1 g. When a liquid dosage form is used, the preparation is typically in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid or nonaqueous liquid suspension.

The compounds of formula I may also be administered topically in the form of a liquid, solid or semi-solid. Liquids include solutions, suspensions and emulsions. Solids include powders, poultices and the like. Semi-solids include creams, ointments, gels and the like.

The amount of a compound of formula I, for the methods of use disclosed herein, vary with the compound chosen, the nature and severity of the condition, and other factors. A representative, topical dose of a compound of formula I is from about 0.01 mg to about 1500 mg, administered one to four, preferably one to two times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient typically comprises about 0.001% to about 90% w/w.

Drops according to the present invention may comprise sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a

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suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%).
5 Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those
10 suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or
15 acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient
20 in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous liquid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid
25 such as steric or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof.
30 Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and other ingredients such as lanolin may also be included.

The methods of the instant invention may also be carried out by delivering the agent parenterally. The term 'parenteral' as used

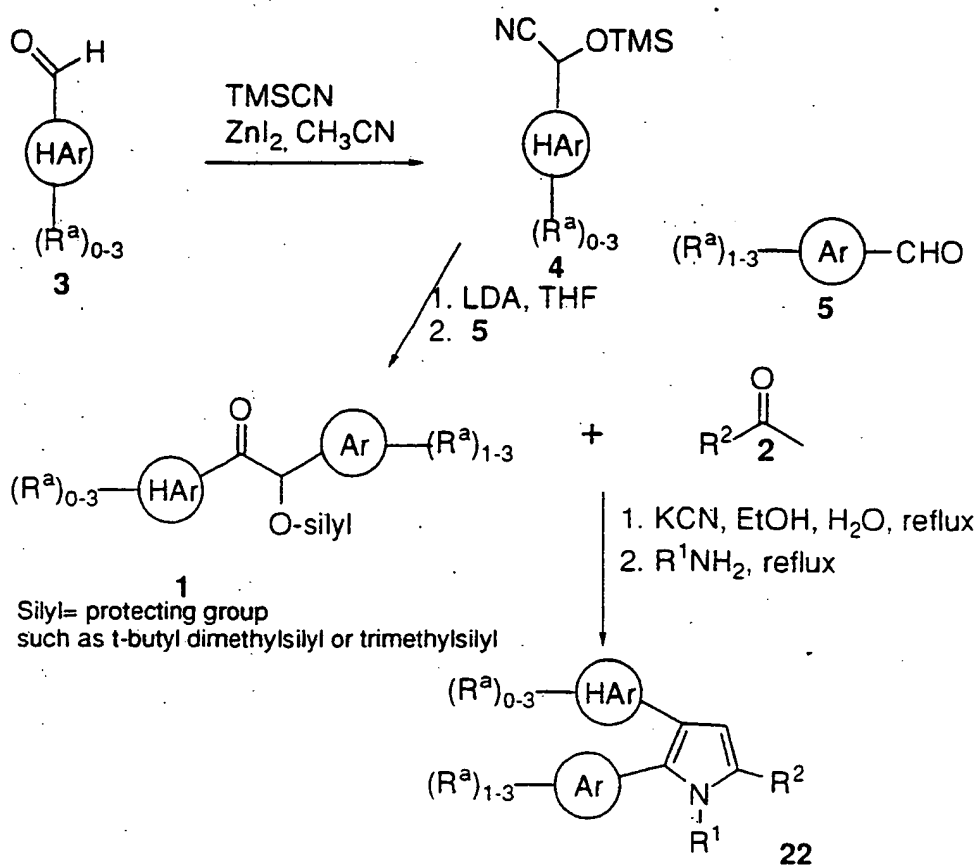
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herein includes intravenous, intramuscular, or intradermal and subcutaneous administration. The intravenous and intramuscular forms of administration are preferred. Appropriate dosage forms for such administration may be prepared as described above. The instant
5 invention can also be carried out by delivering the compounds of formula I intranasally, rectally, transdermally or vaginally.

The compounds of formula I may be administered by inhalation. By 'inhalation' is meant intranasal, pulmonary or oral inhalation administration. Appropriate dosage forms for such
10 administration include an aerosol formulations, e.g., metered dose inhalers and the like..

Compounds of formula I (e.g., compound 22 and 22a) are prepared (see Scheme I) by the reaction of compound 1, or a protected version thereof with an acetophenone (commercially available) in the
15 presence of potassium cyanide followed by treatment with an alkyl or aryl amine, ammonia or equivalent thereof (ammonium acetate) at elevated temperature.

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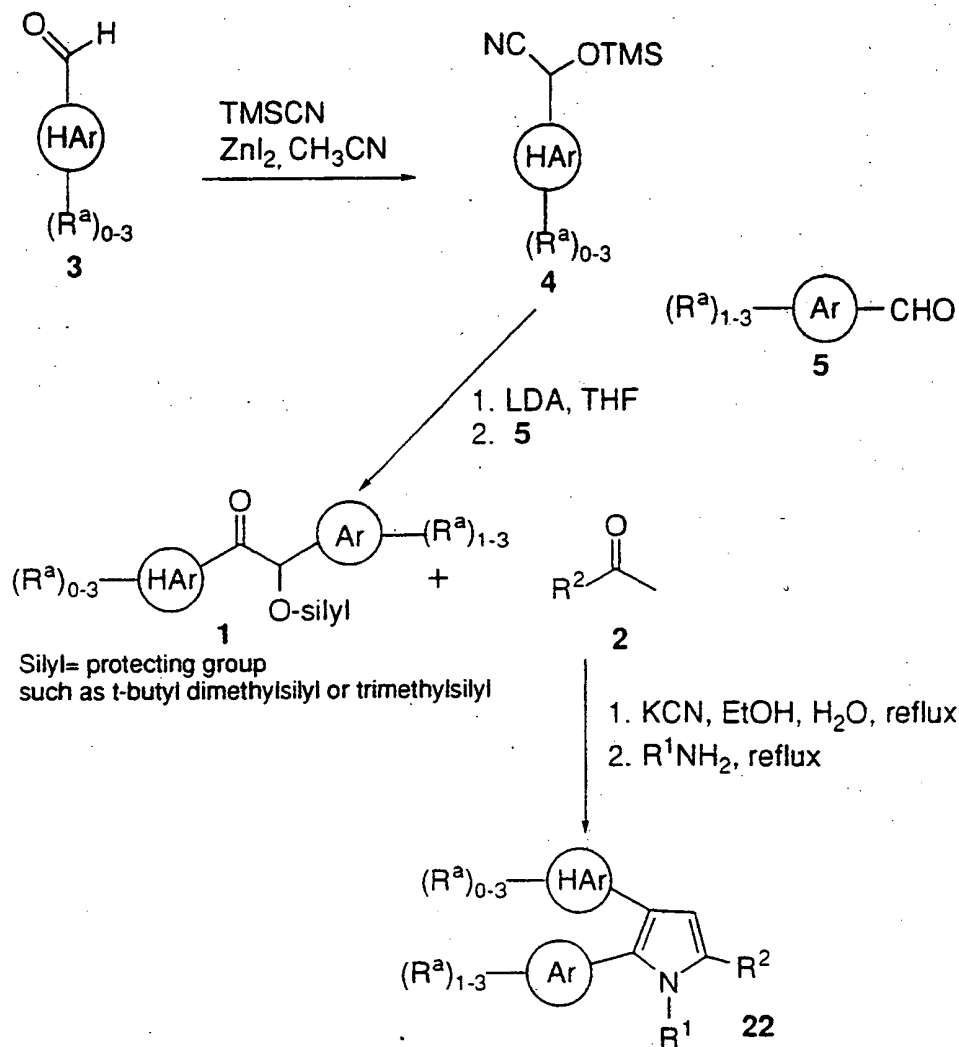
SCHEME I

Compound 1 is prepared as described below.

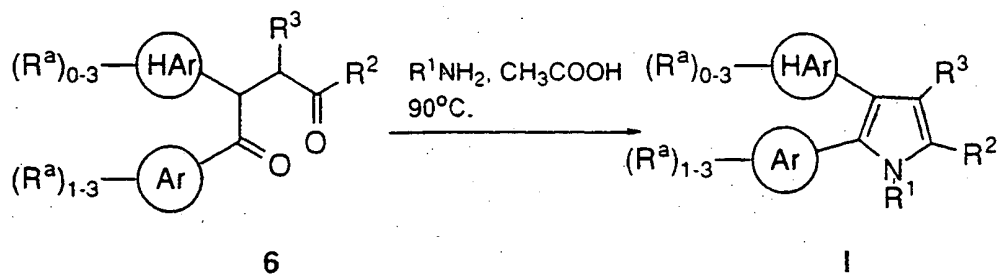
Heteroaromatic aldehydes 3 are converted to their trimethylsilyl cyanohydrins 4. Deprotonation and reaction with an aldehyde 5 provides trimethyl silyl protected benzoin 1 (Hunig, S.; Wehner, G. Chem. Ber. 112, 2062 1979).

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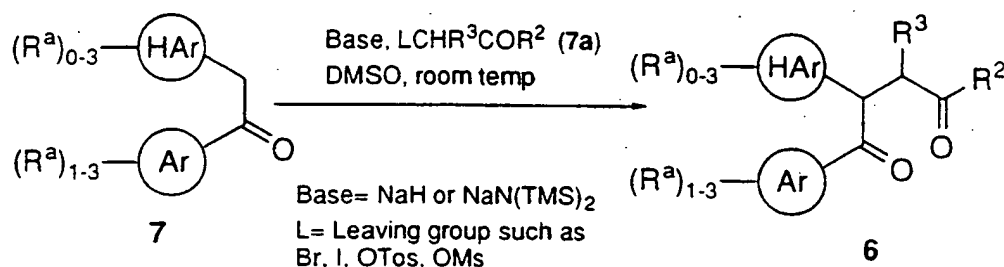


SCHEME II



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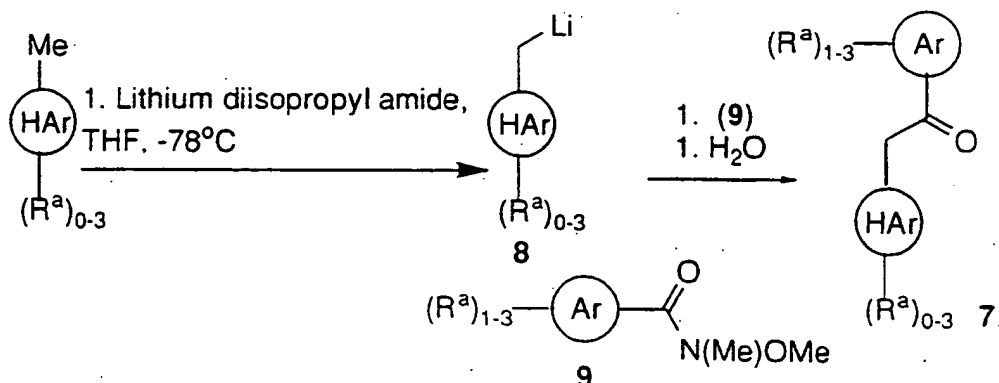
The condensation of a 1,4-diketone with ammonia gives rise to pyrroles (Paal Knor Synthesis). A 1,4-diketone such as 6 is reacted with ammonia (or a compound that gives rise to ammonia such as ammonium acetate) or a primary amine to provide compounds of formula 1 generally in the presence of an acid catalyst such as acetic acid or titanium tetrachloride (See Scheme II). 1,4-diketone 6 is thus regioselectively constructed so that the appropriate groups are present on the pyrrole ring.



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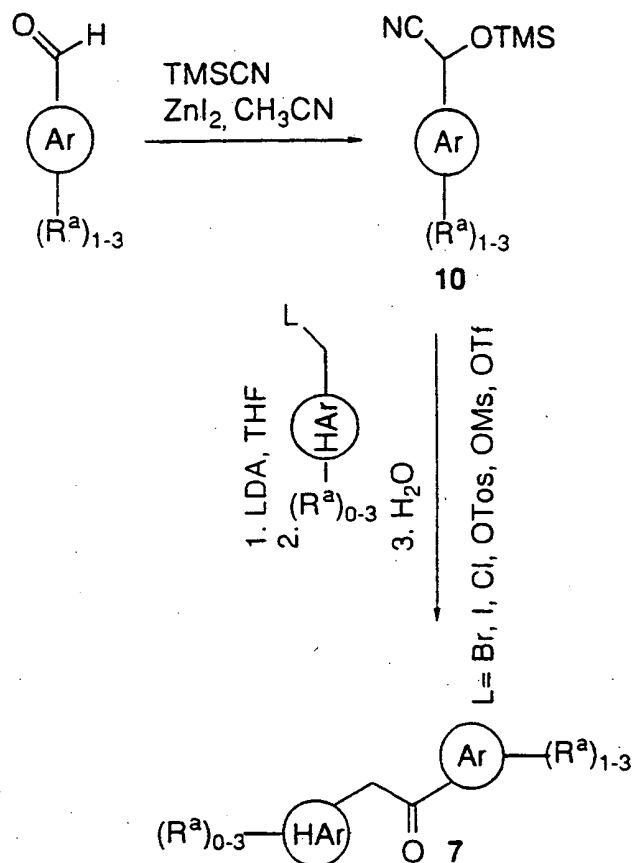
Alkylation of 1-aryl-2-heteroarylethanones 7 with an alpha-leaving group substituted ketone 7a provides 1,4 diketones 6 (Iyer, R. N.; Gopalachari, R. Ind. J. Chem. 11, 1260, (1973)). The alkylating agent 7a is prepared by various methods such as: free radical or acid catalyzed bromination of a ketone; halogenation of a ketone enolate; conversion of the hydroxyl group of an alpha-hydroxy ketone to a leaving group such as the bromide, triflate, tosylate or mesylate.

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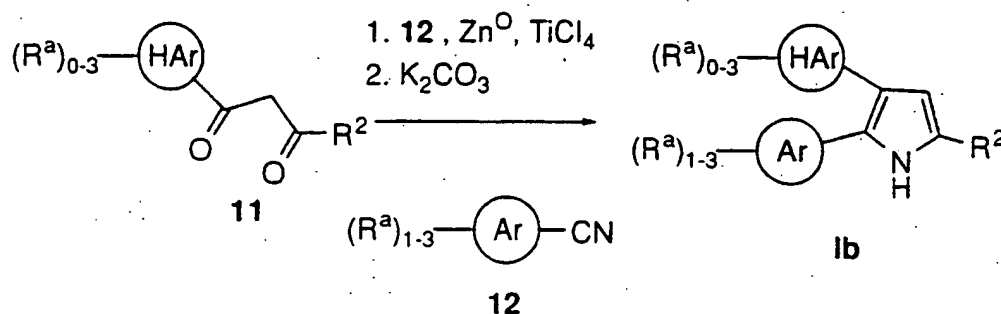
Ethanones **7** are prepared by addition of heteroaryl methyl anions **8** to activated benzoic acids **9** (for example esters, acid chlorides, nitriles and N-methoxy-N-methyl amides) (see: Wolfe, J. F. et al J. Org. Chem. 39, 2006 (1974) and Kaiser, E. M. et al Synthesis 705 (1975) and Ohsawa A. Chem. Pharm. Bull. 26, 3633, (1978)).



10 An alternative approach to Compound **7** is via alkylation of aryl trimethyl silyl protected cyanohydrins **10**. Treatment of **10** with lithium diisopropyl amide in THF and addition of a heteroaryl methyl group functionalized with a leaving group L (for example: Br, I, Cl, tosylate, mesylate) followed by acid catalyzed hydrolysis of the silyl cyanohydrin group provides ethanone **7** (Deuchert, K.; Hertenstein, U.; Hunig, S.; Wehner, G. Chem. Ber. 112, 2045, (1979)).

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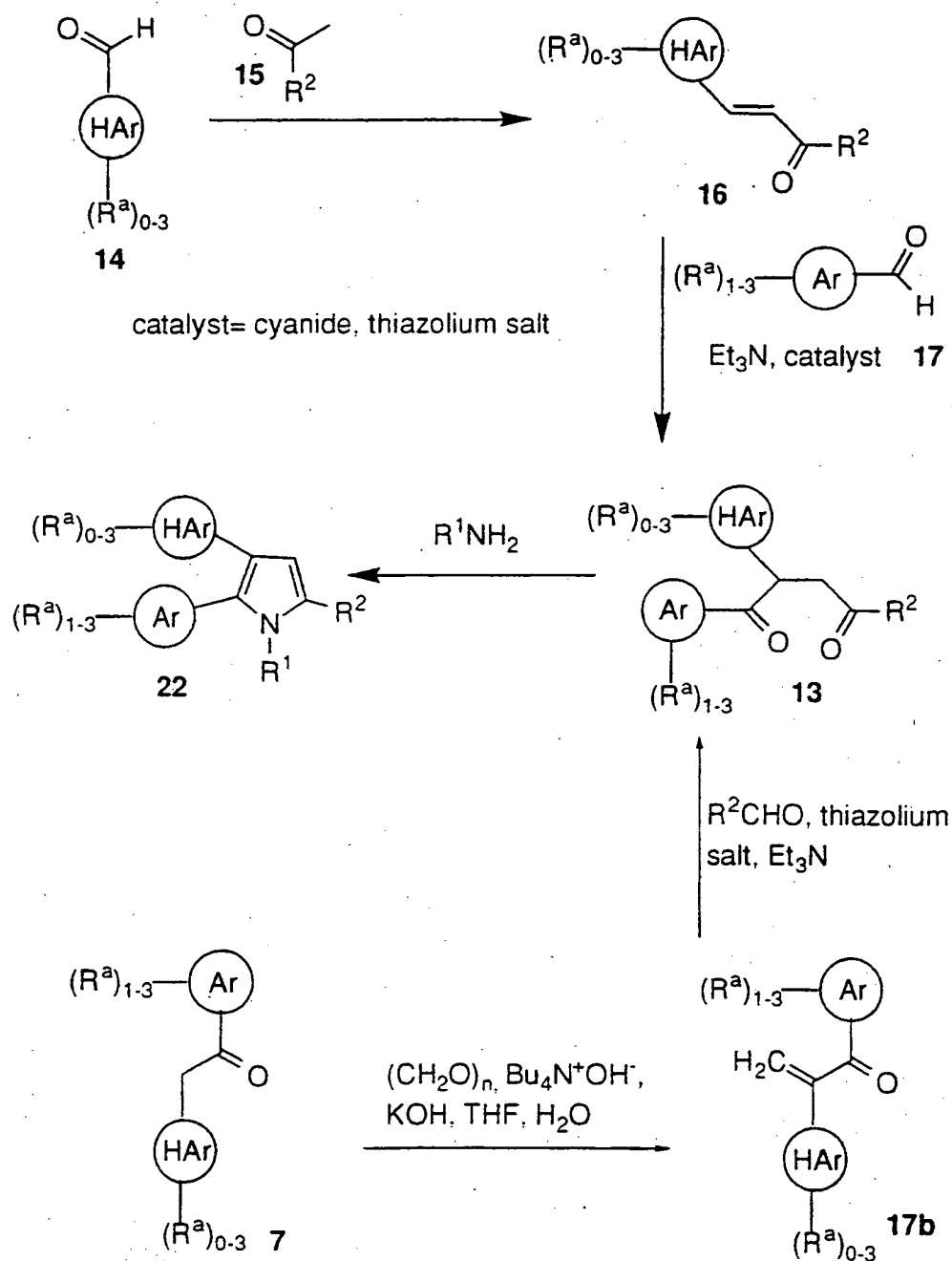
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SCHEME III

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The reductive cross coupling of a 1,3 diketone **11** with a nitrile **12** in the presence of zinc and titanium tetrachloride gives rise to compounds of formula I (Gao, J. Hu, M.; Chen, J.; Yuan, S.; Chen, W. Tet Lett. 34, 1617, (1993)). The 1,3 diketone **11** is prepared by

10 alkylation of **4** with bromoacetophenones (See Scheme III).

SCHEME IV

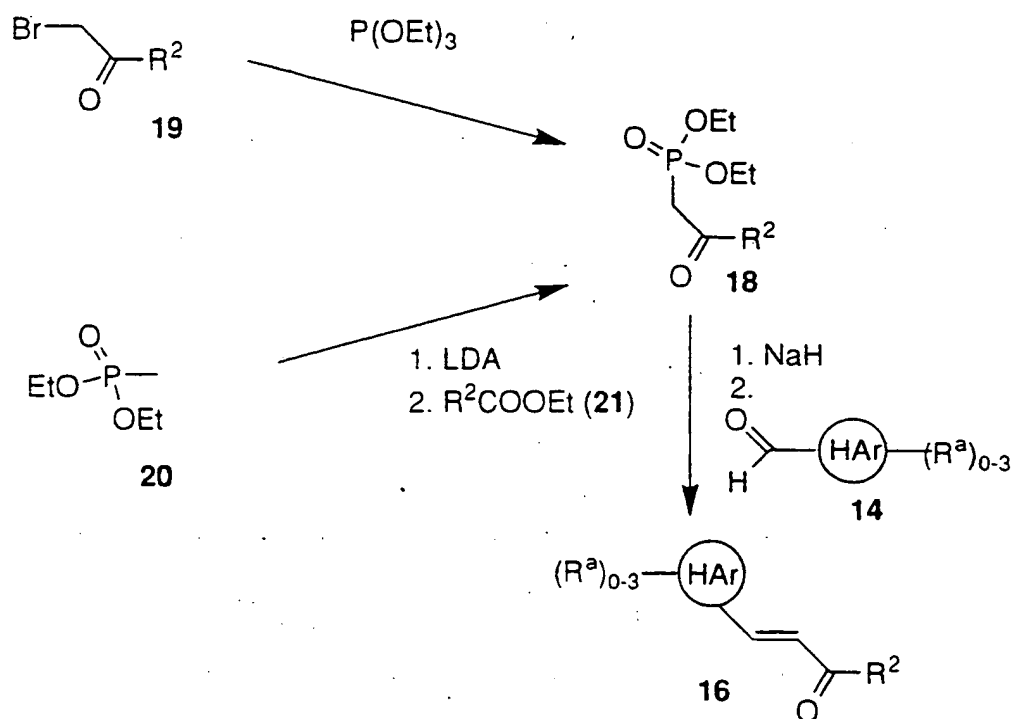
The 1,4-diketone **13** can also be prepared as described below in Scheme IV. A heteroaryl aldehyde **14** is condensed with a

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5 methyl ketone **15** to provide α,β -unsaturated ketone **16**. In the presence of a catalyst such as cyanide or a thiazolium salt, the aryl aldehyde **17** reacts with **16** to give **13** (Stetter, H. J. et al Heterocyclic Chem. **14**, 573, 1977 and Stetter, H. et. al. Organic Reactions, Vol 40, 407-496). Condensation of **13** with an amine provides compounds of formula I.

Alternatively, variations of R^2 may be introduced by addition of R^2 aldehydes to alkenes **17b** that are readily available from the ketones **7** described above.

10 SCHEME V



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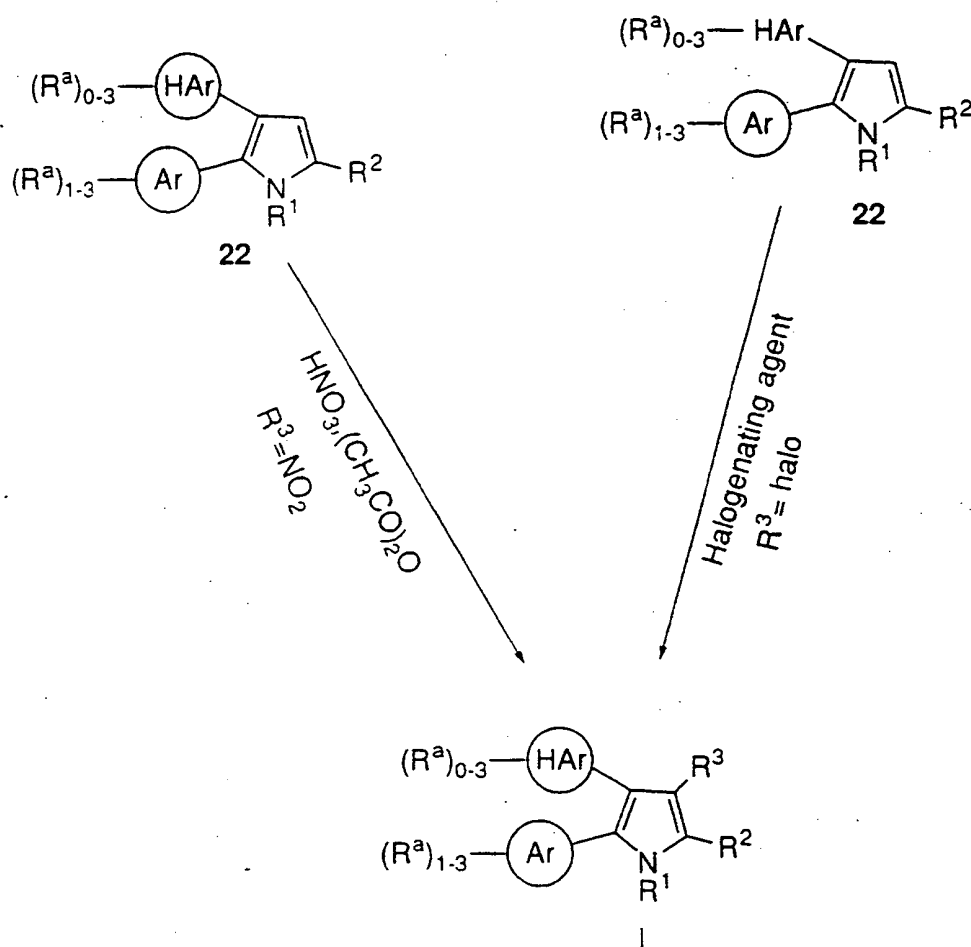
Intermediate **16** is prepared by a Horner-Emmons reaction of the anion of **18** with the heteroaryl aldehyde **14**. The reagent **18** is prepared by reaction of the bromoketone **19** and triethyl phosphite or

- 40 -

by reaction of the lithium salt of diethyl methylphosphonate with an ester **21**.

SCHEME VI

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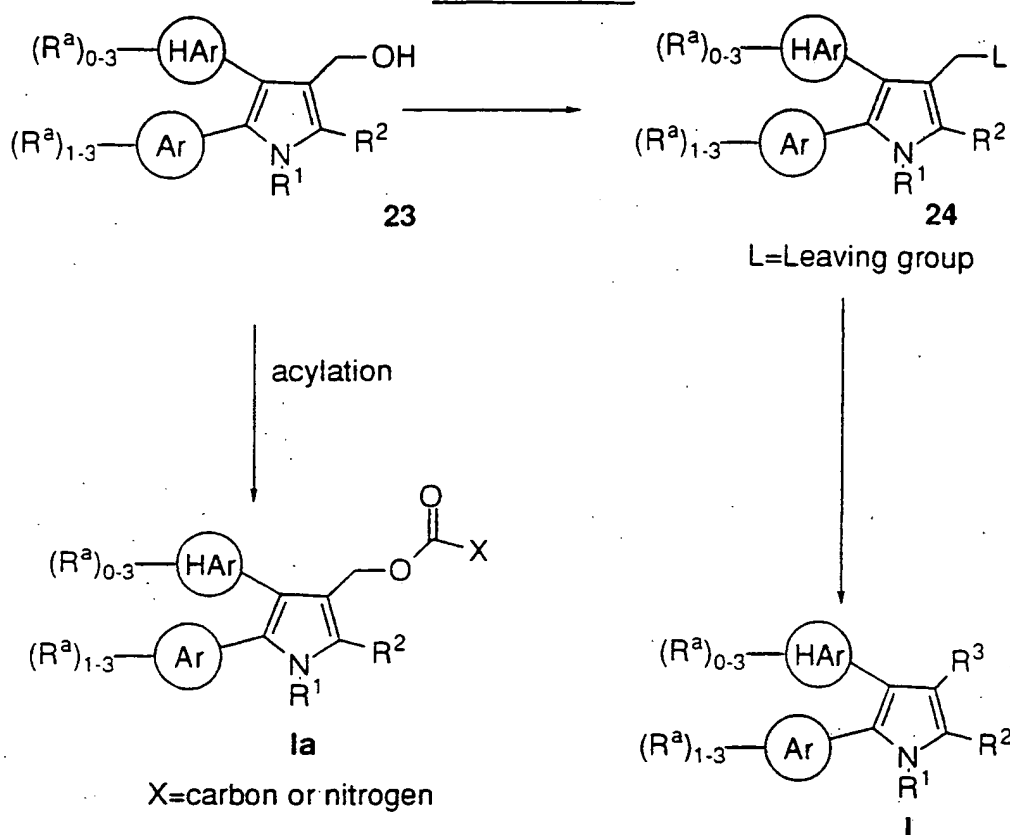


- 10 A nitro group is introduced into the pyrrole nucleus at the R^3 position (generic nomenclature) by electrophilic nitration of a compound such as **22** (or a less advanced intermediate) in the presence of fuming nitric acid and acetic anhydride.

- 15 Halogens may be introduced by electrophilic halogenation with reagents such as XeF_2 ($R^3=F$), N-chlorosuccinimide in DMF ($R^3=Cl$), N-bromosuccinimide in DMF ($R^3=Br$), I_2 in KI ($R^3=I$). Other

reagents are available to carry out this conversion, the choice of reagent being dependent on the presence of functional groups that may be sensitive to the reagent being utilized. See, e.g. Pyrroles Part I, R. Alan Jones, ed., Heterocyclic Compounds, Vol 48 Part I, John Wiley, New York, 1990. Pages 348-391.

SCHEME VII

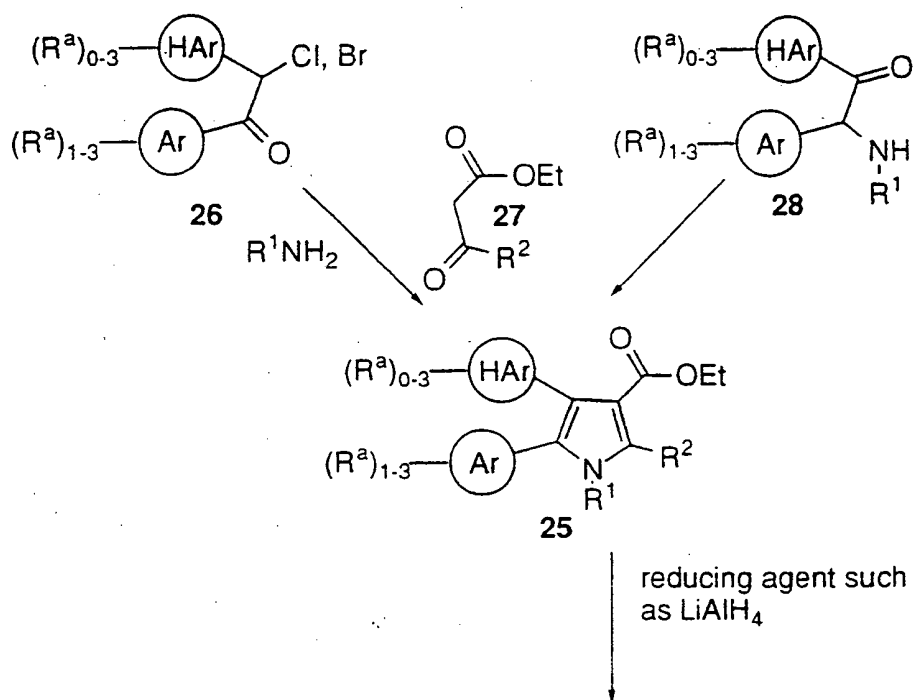


Introduction of alkyl and heterocyclyl alkyl groups at the 3 position is described. Direct introduction is possible as described in the use of 1,4 diketone **6** as a precursor of compounds of formula Ia as described above. The preparation of the pyrrole **23** containing a hydroxymethyl group at position provides an intermediate that is readily elaborated into compounds of formula I.

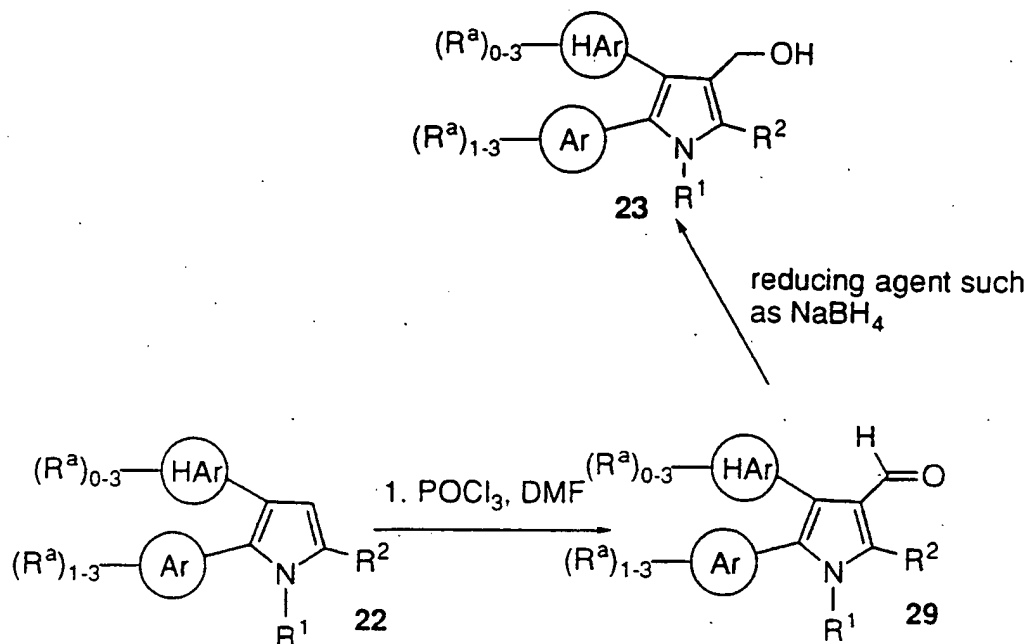
Acylation of the hydroxyl group with activated acids an isocyanates provides esters and carbamates respectively of formula I. Conversion of the hydroxy group into a leaving group **24** (for example

Br, I, Cl, triflate etc.) enables the introduction of alkyl, heterocyclyl and amines and thiol groups by displacement with a nucleophile. Suitable nucleophiles include, for example, an alkyl or heterocyclyl anion, a primary or secondary amine or a thiol.

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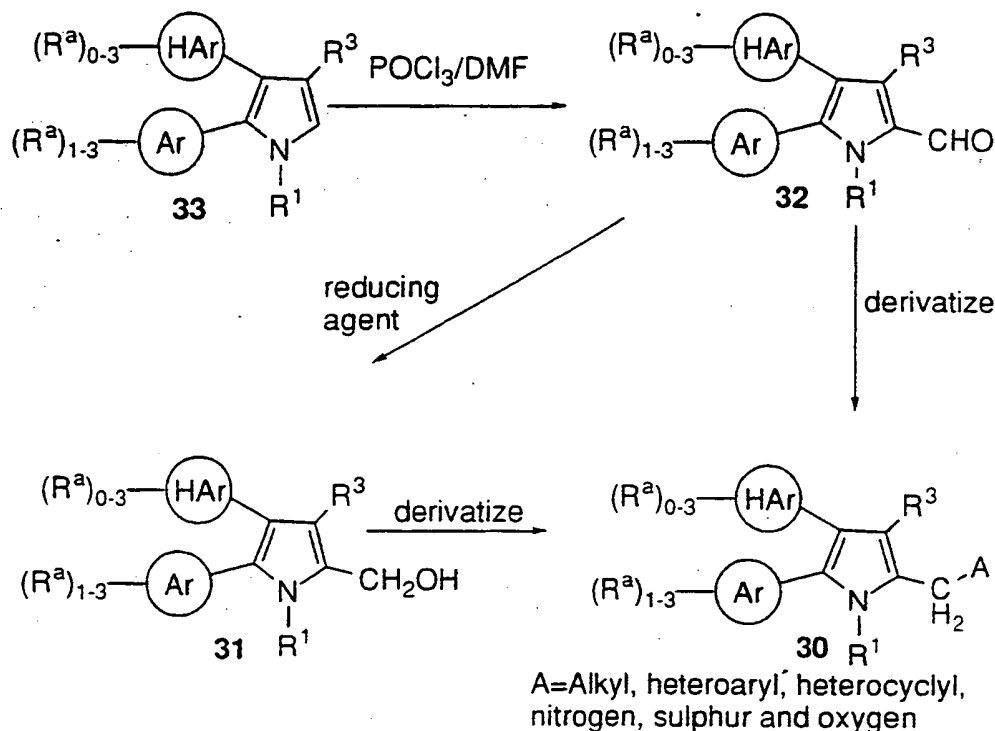
SCHEME VIII

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Hydroxymethyl substituted pyrroles **23** are prepared by reduction of esters **25** through the reaction with a reducing agent such as lithium aluminum hydride. The ester **25** are prepared by treatment of 1,2 -disubstituted-2 halo ketones **26** with 3-keto esters **27** and ammonia or an amine producing ester **25** (Hantzsch. Ber. Dtsch. Chem. Ges. **23**, 1474, **1890**). Alternatively a 2-amino ketone **28** reacts with a 3-keto ester **27** to produce **25**.

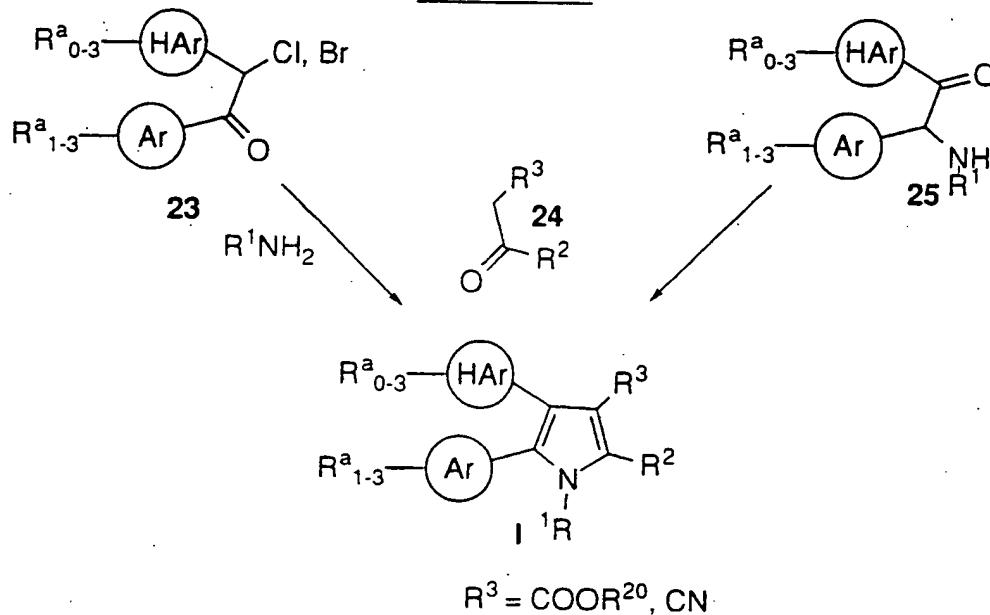
A further method of synthesis of **23** is the reduction of the aldehyde **29** with a reducing agent such as sodium borohydride. The aldehyde is prepared by treatment of the R^3 -unsubstituted pyrrole with the Vilsmeier reagent (POCl_3/DMF).

SCHEME IX

- Variation of R^2 groups may be achieved as shown in Scheme IX. Alkyl, heteroaryl, heterocyclyl and heteroatom and heteroatom substituted alkyl, heteroaryl, heterocyclyl groups are introduced through the displacement of a leaving group derived from the hydroxyl group in **31**. The allylic nature of a leaving group (such as bromide, chloride, mesylate, tosylate and triflate etc.) at this position make it very prone to displacement by amines; thiols; alkoxides; aryl, alkyl, heteroaryl and heterocyclyl anions. Furthermore this type of functional group is utilized in organometallic coupling reactions. The alcohol is prepared from the aldehyde **32** by reduction with a reducing agent such as sodium borohydride. The aldehyde **32** is converted to **30** reductive alkylation ($\text{A} = \text{amino}$). The aldehyde **32** is reacted with alkyl, aryl, heteroaryl and heterocyclyl anions to give secondary alcohols. These are dehydrated and reduced to give further analogs of formula I. Aldehydes **32** are available by hydrolysis of acetals that have been

introduced in one of the schemes above or via reaction of the unsubstituted pyrrole **33** with Vilsmeier reagent (DMF/ POCl_3).

5

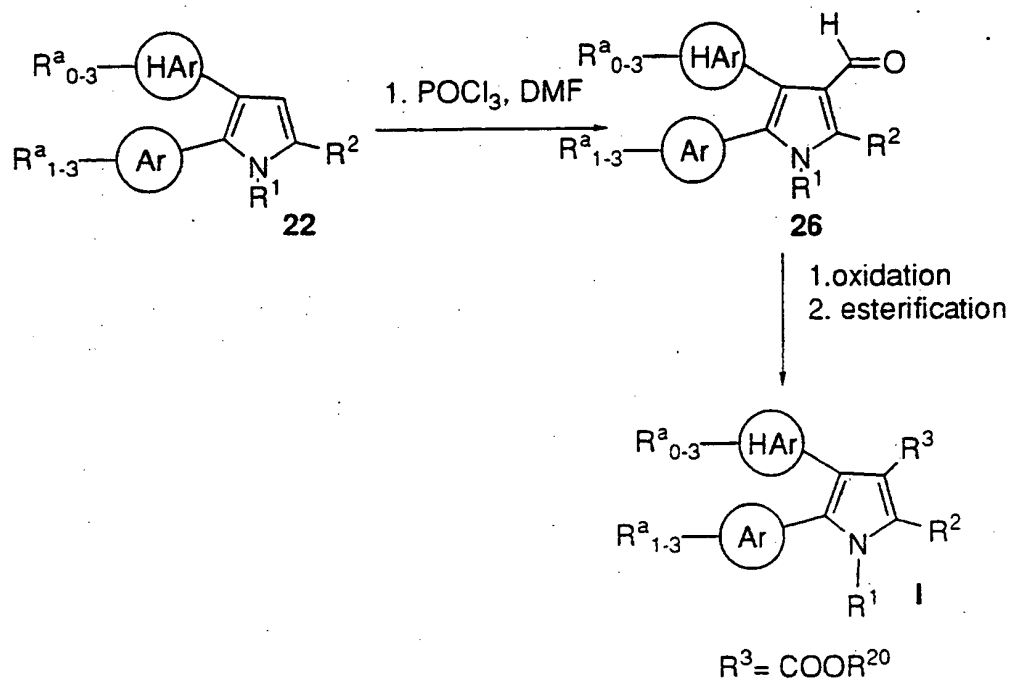
SCHEME X

The ester and nitrile of formula **I** may be prepared as shown in Scheme X by treatment of 1,2 disubstituted-2 halo ketones **23** with **24** with ammonia or an amine producing ester **I** (Hantzsch. Ber. Dtsch. Chem. Ges. **23**, 1474, **1890**). Alternatively a 2-amino ketone **25** reacts with **24** to produce **I**.

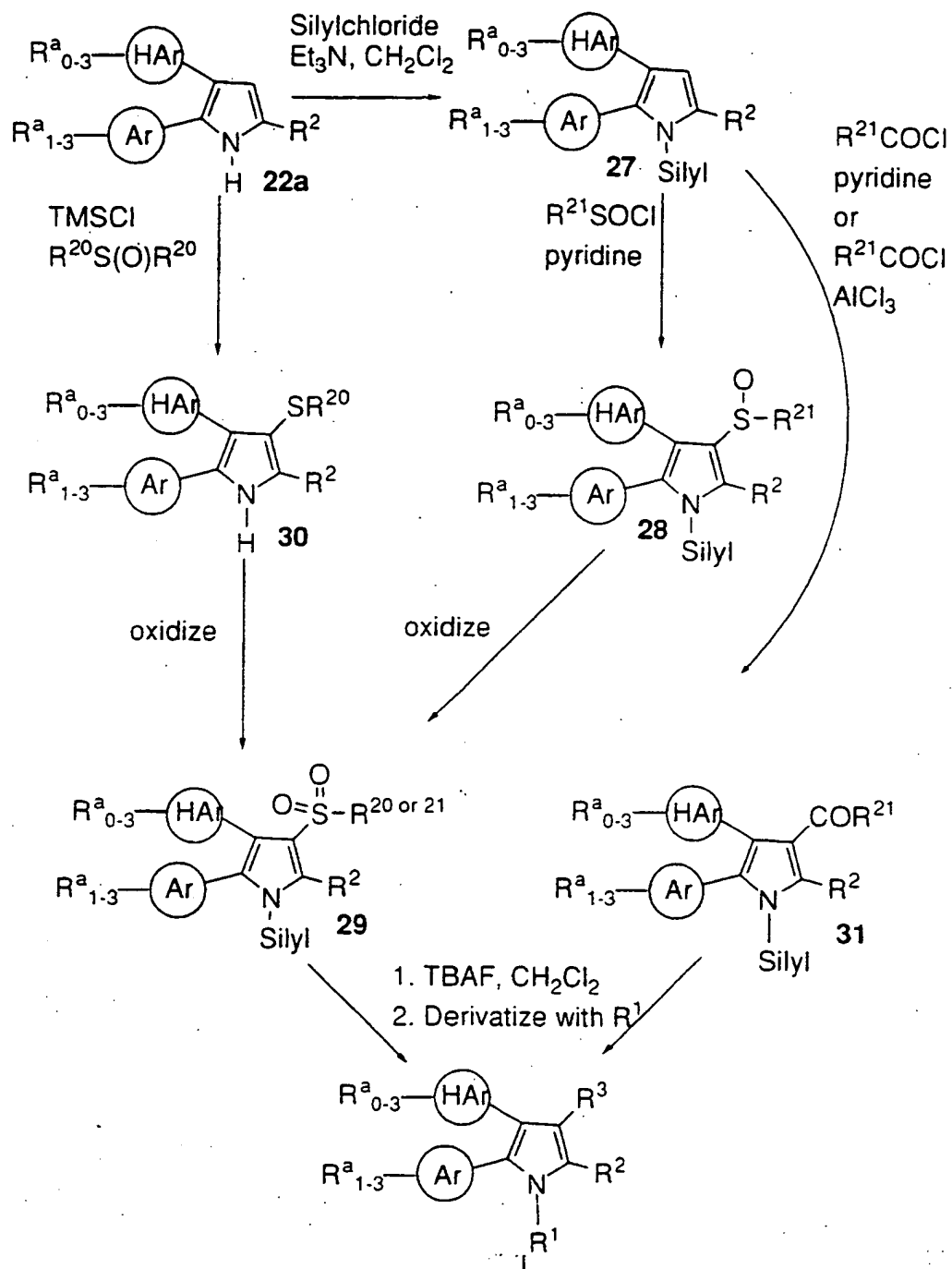
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- 46 -

SCHEME XI



- A further method of synthesis of Compounds of formula I is by oxidation and esterification of aldehyde 26. The aldehyde is prepared by treatment of the R³-unsubstituted pyrrole 22 with the Vilsmeier reagent (POCl₃/DMF). See Scheme XI.
- 5

SCHEME XII

- 48 -

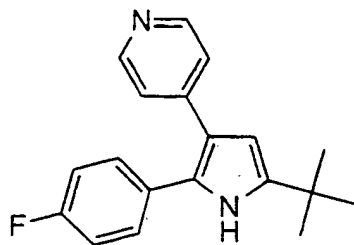
The pyrrole 22a may be silylated on nitrogen to give 27 by treatment with a silyl chloride and base in a solvent such as methylene chloride. The pyrrole 27 may then be sulphonylated with a sulphonylchloride under basic conditions to provide 28 (J. Org Chem 6317, 1990). Oxidation of 28 with a reagent such as m-chloroperoxybenzoic acid or potassium persulfate will give the sulphone 29. Removal of the silyl group and derivatization of the pyrrole will give compounds of Formula I. 22a may also be converted to the sulphide 30 by reaction of 22 with a symmetrical sulfoxide in the presence of trimethylsilylchloride to give 30. Oxidation of 30 with a reagent such as m-chloroperoxybenzoic acid will give 29. The silyl pyrrole 27 may also be acylated with an acid chloride to give the ketone 31. Removal of the silyl group from 31 and derivatization of the pyrrole will give compounds of Formula I. Pyrroles such as 22 may also be sulphonylated directly without N-protection, by treatment with sulphonyl chlorides in a solvent such as dichloromethane at 0°C (J. Org. Chem. 5336, 1980). Oxidation as described above may provide pyrroles of Formula I where R³ is SO₂R²¹. See Scheme XII.

- 55 -

A mixture of 0.15 g (0.79 mmol) of the product of Step 1, above, 0.098 g (0.79 mmol) of 4-fluorobenzaldehyde, 20 mg of 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide and 0.05 g (0.39 mmol) of triethylamine was heated to 80°C for 3 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo. The product was purified by medium pressure liquid chromatography over silica gel to give the product.

¹H-NMR (CDCl₃, 300 MHz): 1.17 (s, 9H); 2.82 (dd, 1H); 3.67 (dd, 1H); 5.04 (dd, 1H); 7.06 (t, 2H); 7.19 (d, 2H); 7.97 (dd, 2H); 8.50 (d, 2H).

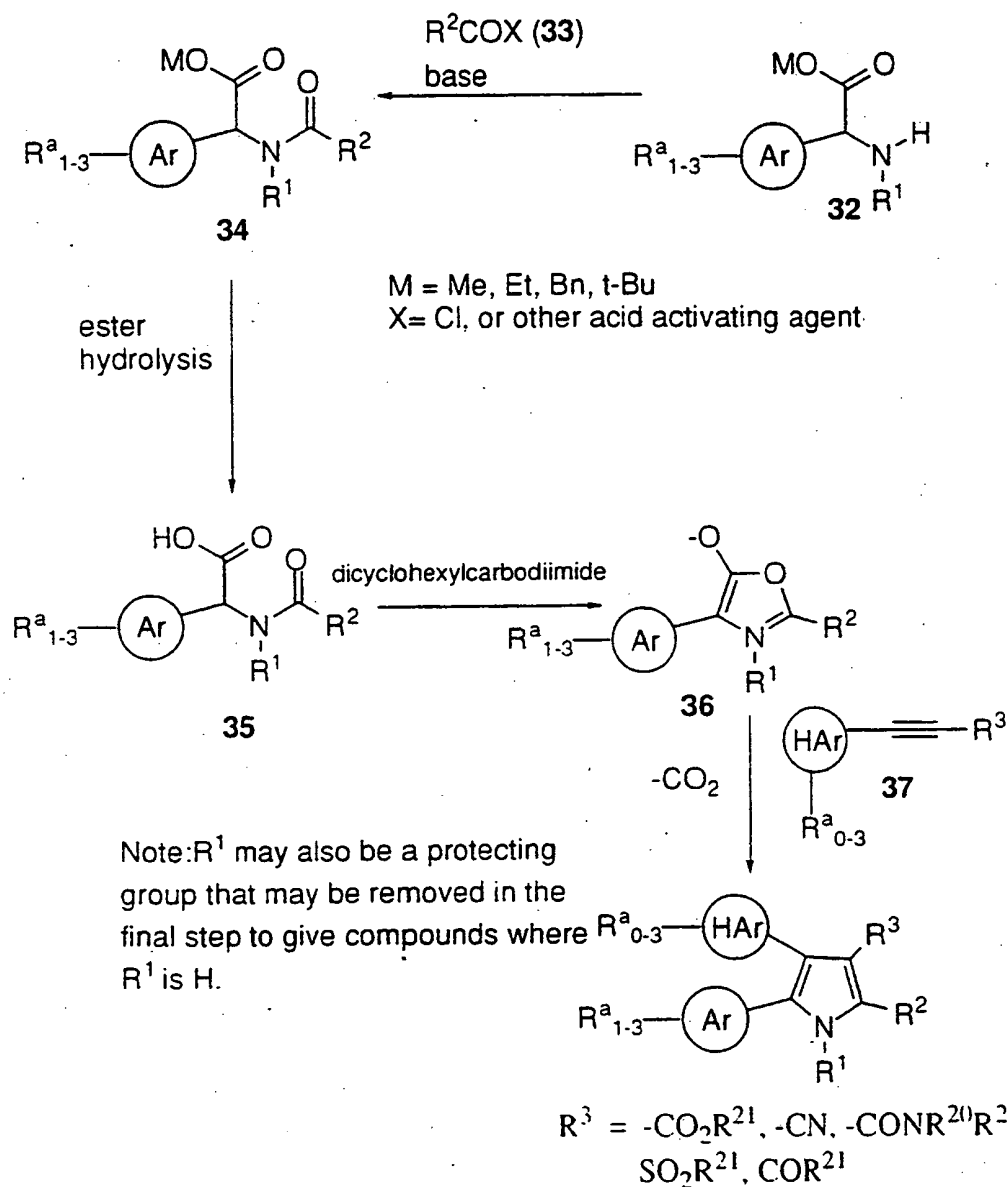
Step 3



The product of Step 2 was dissolved in 1.0 mL of acetic acid (AcOH) and was treated with 0.5 g of ammonium acetate. The reaction mixture was heated to 110°C for 1 hour. The reaction mixture was cooled to room temperature and diluted with 25 mL of ethyl acetate and was washed with 3 x 10 mL of water and 1 x 10 mL of brine. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by rotary chromatography over silica gel eluting with 2% MeOH/CH₂Cl₂.

¹H-NMR (CDCl₃, 300 MHz): 1.35 (s, 9H); 6.19 (d, 1H); 7.05 (t, 2H); 7.20 (m, 2H); 7.25-7.36 (m, 2H); 8.03 (bs, 1H); 8.41 (d, 2H).

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SCHEME XIII

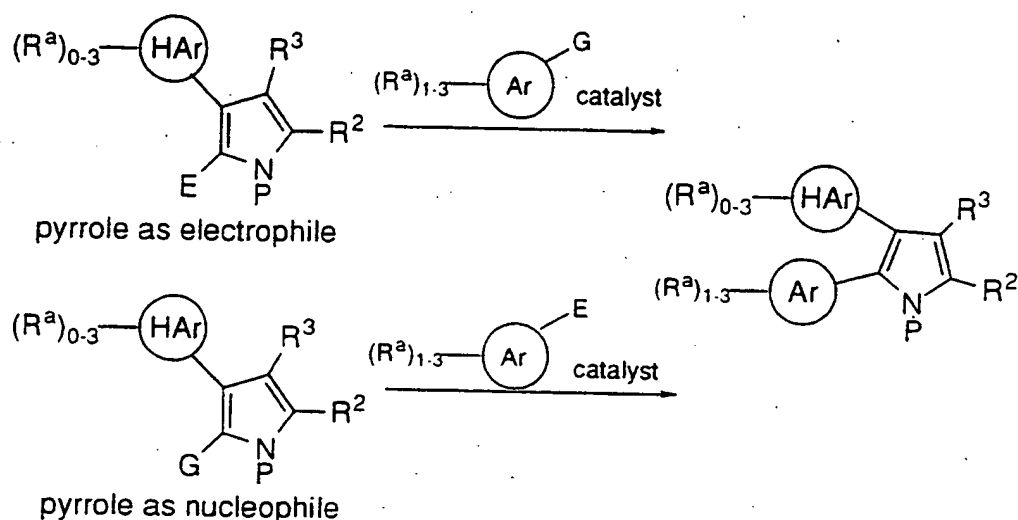
I

The amino acid ester 32 may be acylated with an acid 33 that is suitably activated (acid chloride or other activating group used in amide coupling reactions) to give 34. Hydrolysis of the ester protecting group will provide 35. Cyclization by treatment with an acid activating

group such as DCC will give the oxazolium species 36. Addition of an alkyne 37 to 36 may give a pyrrole of Formula I via a 3+2 cycloaddition followed by loss of carbon dioxide. Various R³ groups may be incorporated in this manner. See Scheme XIII.

5

SCHEME XIV



E = Br, I, OSO₂CF₃

G = SnMe₃, B(OH)₂, ZnCl, MgBr

catalyst = Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂

P = R¹ or protecting group such as trialkyl silyl, benzyl, substituted benzyl, t-butyloxycarbonyl

10

Aryl and heteroaryl rings are appended to the pyrrole ring system by utilization of organometallic coupling technology (Kalinin, V. Synthesis 413 1991). Two alternative approaches are utilized for appending aryl and heteroaryl rings to the pyrrole ring. The pyrrole ring functions as the electrophile or as the nucleophile.

15

Any of the two appended aromatic or heteroaromatic rings is attached to the pyrrole ring system. (Alvarez, A. J. et al J. Org. Chem. 1653, (1992) (use of boronic acid and tributyl stannanes for coupling to aromatic and heteroaromatic rings)). Attachment of pyrrole pendant groups is carried out with or without other Ar, HAr, R² or R³

groups attached. R² groups are introduced through the use of the Heck reaction (Heck, R. F.Org. React. (1982), 27, 345) in which alkenes are coupled with heteroaryl halides. Alkynes are coupled with heteroaryl halides to give alkyne substituents at R². These R²=alkene and alkyne groups may, in turn be reduced to alkanes by hydrogenation.

The synthesis of pyrroles containing nucleophilic groups for coupling reactions depends on the pyrrole substitution pattern. Lithium anions are prepared by metalation of a regioselectively halogenated pyrrole, or the regioselective deprotonation of the pyrrole preferably by the use of a directing functional group. The resulting anion may then be trapped by a trialkyl stannyl halide or a trialkyl borate or transmetalated to magnesium or zinc by treatment with appropriate halide salts. A further method used to incorporate a trialkyl stannyl group is the coupling of a bromo, iodo or triflate substituted pyrrole with hexaalkylditin in the presence of a palladium catalyst.

The synthesis of pyrroles incorporating electrophilic groups may be carried out by the regioselective halogenation of a pyrrole (Pyrroles Part 1, R. Alan Jones,ed., Heterocyclic Compounds, Vol 48 Part 1, John Wiley, New York, 349-391,(1990)). The regioselectivity of halogenation will depend on the size, nature and substitution position on the pyrrole ring as well as the presence or absence of the N-alkyl protecting group. Triflates may be prepared by acylation of hydroxy pyrroles with triflic anhydride.

The reaction conditions used will depend on the nature of the coupling species. In the case of magnesium, zinc and stannyl coupling reactions the solvent used is normally toluene or DMF under anhydrous conditions. In the case of boronic acid couplings, a heterogenous system is used of water, toluene, dimethoxyethane or ethanol in the presence of a base such as sodium carbonate or bicarbonate. In general the reaction takes place at an elevated temperature (80-100 °C). Catalysts used depend on the structure of the components to be coupled as well as the functional groups. Most commonly, tetrakis(triphenyl)phosphinepalladium (0) or palladium bis(triphenyl phosphine dichloride are utilized.

The preparation of 4-halo substituted pyrroles may be accomplished by treatment of 2,3,5, trisubstituted pyrroles with halogens. Alkyl substituents at the 4 position of the pyrrole may be introduced through the synthesis of the 1,2,3,4-tetrasubstituted 1,4-diketone followed by cyclization with ammonia or an amine. Alternatively, coupling of alkenes or alkynes with 4-halo pyrroles (Heck reaction, see Kalinin, V. Synthesis 413 (1991) for a review) will give rise to alkenyl and alkynyl substituted pyrroles that may be reduced or otherwise modified to provide compounds of formula I.

Functional groups such as halogens, sulfides, nitro groups, ethers and other groups stable to the reaction conditions used in the linear synthesis of the pyrroles are incorporated in the initial steps of the reaction sequence. Sulfides may be oxidized to sulfoxides and sulfones with reagents such as m-chloroperbenzoic acid. Sulfides may also be converted to sulfonyl chlorides by oxidation and chlorination by chlorine in water.

Primary amines are prepared from nitro groups by catalytic (Pd/C, H₂ or Raney Nickel, H₂) or chemical means (CoCl₂, NaBH₄). Alkylation of amines to give secondary and tertiary amines is achieved by reductive alkylation (aldehyde, NaCNBH₄) or alkylation with an alkyl group substituted with a leaving group in the presence of a base such as K₂CO₃. Tertiary amines may, alternatively, be carried through the reaction sequence to the pyrroles. Acylation of primary or secondary amines with activated acids, chloroformates, isocyanates and chlorosulfonates will give rise to amides, carbamates, ureas and sulfonamides, respectively.

Other methods of preparing amides and ureas are useful; such as for example, treatment of the amine with phosgene, or an equivalent thereof, followed by acylation of an alcohol or amine with the intermediate activated chloroformamide.

Carboxylic acids are best introduced as esters early in the synthesis. Saponification will provide carboxylic acids. Transesterification or esterification of the acids will give esters. Carboxylic acids may be converted to amides by activation and reaction

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with amines. Phenols are best introduced in a protected form early in the synthetic sequence to the pyrrole. Removal of the protecting group provides a phenol which may subsequently be alkylated in the presence of an alkylating agent and base to give an ether, or acylated with an isocyanate to give carbamates. Phenols may be converted to aryl ethers by reaction with an aryl bismuthane in the presence of copper II acetate.

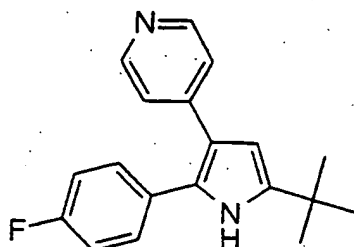
Aryl and heteroaryl groups may be attached to pyrrole pendant aryl and heteroaryl groups by application of coupling chemistry technology as outlined above.

All of the above secondary conversions are well known to one skilled in the art. The sequence and conditions of the reaction steps is dependent on the structure and functional groups present. Protecting groups may be necessary and may be chosen with reference to Greene, T.W., et al., Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., 1991. The blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with fluoride ion, treatment with a transition metal catalyst and a nucleophile, and catalytic hydrogenation.

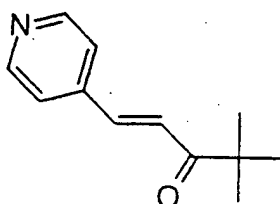
Examples of suitable hydroxyl protecting groups are: trimethylsilyl, triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, t-butyldiphenylsilyl, t-butyldimethylsilyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, and allyloxycarbonyl. Examples of suitable carboxyl protecting groups are benzhydryl, o-nitrobenzyl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyldimethylsilyl, t-butldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl, p-methoxyphenyl, 4-pyridylmethyl and t-butyl.

The following examples are illustrative and are not limiting of the compounds of this invention.

- 54 -

EXAMPLE 12-(4-fluorophenyl)-5-(t-butyl)-3-(4-pyridyl)-pyrrole

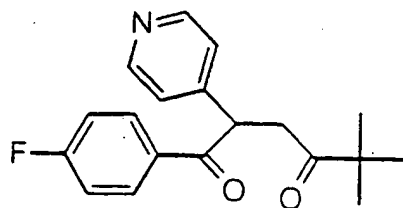
5

Step 1

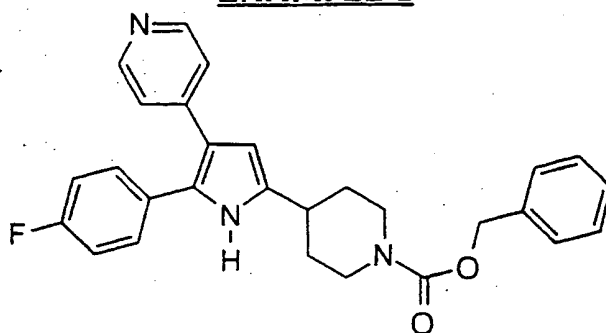
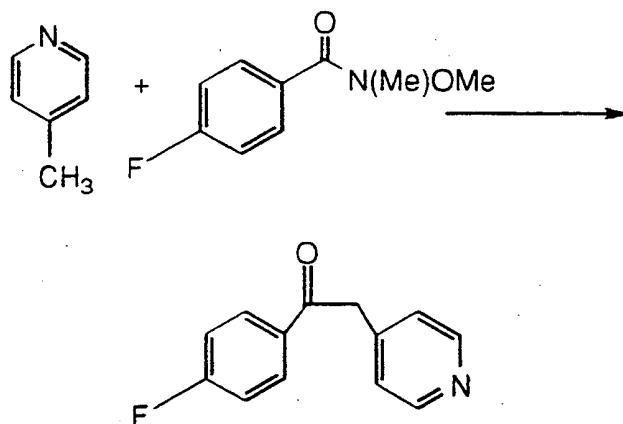
- To a solution of 10 g (0.25 m) of sodium hydroxide in 150 ml of ethanol was added a mixture of 5 g (0.05 m) pinacolone and 5.35 g (0.05 m) of 4-pyridaldehyde in 10 ml of ethanol. After 3 hours the reaction mixture was diluted with 300 mL of EtOAc and 100 ml of water. The phases were separated and the organic phase was washed with water (2 x 100 ml) and brine (100 ml) and dried over MgSO₄.
- The mixture was filtered and the filtrate was dried in vacuo. The product was purified by crystallization from ethanol and water.

¹H-NMR (CDCl₃, 300 MHz): 1.22 (s, 9H); 7.26 (d, 1H); 7.41 (m, 2H); 7.56 (d, 1H); 8.74 (m, 1H).

20

Step 2

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EXAMPLE 22-(4-fluorophenyl)-5-(n-(CBz)-piperidin-4-yl)-3-(4-pyridyl)-pyrrole5 Step 11-(4-fluorophenyl)-2-(4-pyridyl)-ethanone

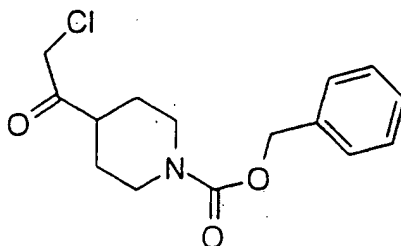
- 10 To a solution of lithium diisopropyl amide (Aldrich Chemical Co. 2.0 M in heptane, THF ethyl benzene) 3.1 mL (6.3 mmol) in 6 mL of anhydrous THF at -78°C under nitrogen was added 0.5 g (5.3 mmol) of 4-picoline dropwise. The reaction mixture was stirred for 20 minutes and then treated with a solution of 0.9 g (5.3 mmol) of
- 15 4-fluoro-(N-methyl-N-methoxy)-benzamide in THF. The reaction mixture was warmed to 0°C and quenched by addition of 10 mL of brine. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried over MgSO₄. The mixture was

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filtered and the filtrate was concentrated in vacuo to give the title compound as an orange solid.

^1H NMR (CDCl_3 300 MHz): 4.23 s (d, 2H), 7.1-7.18 m (4H), 8.02 (dd, 2H), 8.55 (dd, 2H).

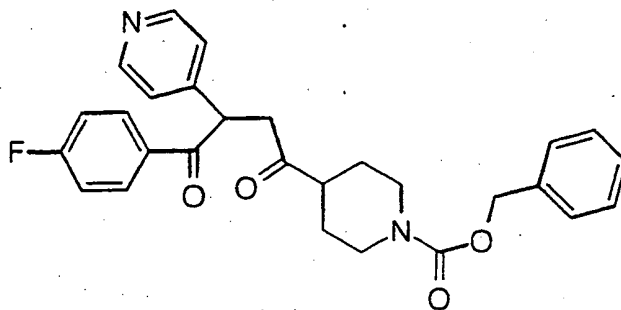
Step 2



To a solution of N-carboxybenzyl-piperidine-4 carboxylic acid (2.0 g (7.6 mmol)) in 15 ml of dry toluene at room temperature was added 2 drops of DMF followed by the dropwise addition of 1.05 g of oxalyl chloride. The reaction mixture was stirred overnight at room temperature. Vacuum was applied to draw off excess HCl and oxalyl chloride and the solution was concentrated in vacuo to provide the acid chloride. The material was dissolved in 20ml of ether and was cooled to 0°C in a dry Erlenmeyer flask. The solution was treated with an ethereal solution of diazomethane prepared from 5 g of N-nitrosomethylurea. The solution was stirred for 20 minutes and was then treated with 8 ml of a 1M solution of HCl in ether. The reaction mixture was stirred for 30 minutes and was then diluted with 20 ml of ethyl acetate and 10 ml of a saturated solution of NaHCO_3 . The phases were separated and the organic phase was washed with water and brine and was dried over MgSO_4 . The mixture was filtered and the filtrate was concentrated in vacuo to give the desired product.

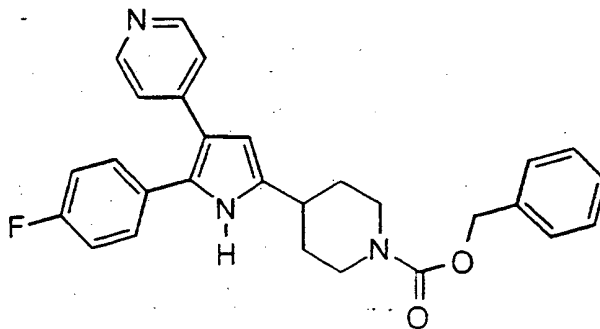
^1H -NMR (CDCl_3 , 300 MHz): 1.56 (m, 2H); 1.85 (bm, 2H); 2.87 (m, 3H); 4.12 (s, 2H); 4.20 (bs, 1H); 5.12 (bs, 2H); 7.35 (m, 5H).

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Step 3

To a solution of the product of Step 1 (0.5 g (2.3 mmol)) in
5 5.0 ml of dry DMSO was added 2.4 ml (2.4 mmol) of a 1M solution of
sodium hexamethyldisilazide in THF. After 10 minutes, a solution of
0.72 g (2.4 mmol) of the product of Step 2 was added in 1 ml DMSO
dropwise. The reaction mixture was stirred for 2 hours, diluted with
EtOAc (20 ml) and washed with water (3 x 10 ml). The combined
10 organic phases were washed with brine and dried over MgSO₄. The
mixture was filtered and the filtrate was concentrated in vacuo. The
residue was purified by MPLC over silica gel eluting with 2%
MeOH/CH₂Cl₂ to give the desired product.
FAB ms: C₂₈H₂₇N₂O₄F:474; Observed: 475 (M⁺+1).

15

Step 4

20

The product of Step 3 was heated in 5 ml of acetic acid in
the presence of 2.0 g ammonium acetate at 110°C for 1.5 hours. The

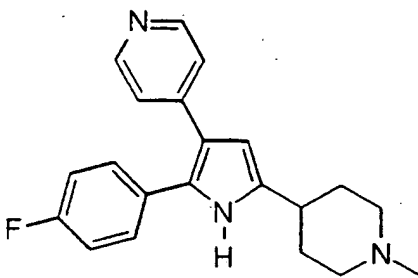
- 59 -

reaction mixture was diluted with EtOAc (10 mL) and washed with water. The combined organic phases were washed with brine and dried over MgSO₄. The mixture was filtered and the filtrate was

concentrated in vacuo. The residue was purified by MPLC over silica gel eluting with 2% MeOH/CH₂Cl₂ to give the desired product.
5 ¹H-NMR (CDCl₃, 300 MHz): 1.67 (m, 2H); 2.02 (bd, 2h); 2.75-3.0 (m, 3H); 4.29 bd, 2H); 5.12 (s, 2H); 6.19 (d, 1H); 7.03 (t, 2H); 7.18 (dd, 2H); 7.25-7.39 (m, 6H); 8.39 (dd, 2H); 8.52 (bs, 1H). FAB ms: C₂₈H₂₆N₃O₂F:455; Observed: 456 (M⁺+1).

10

EXAMPLE 3

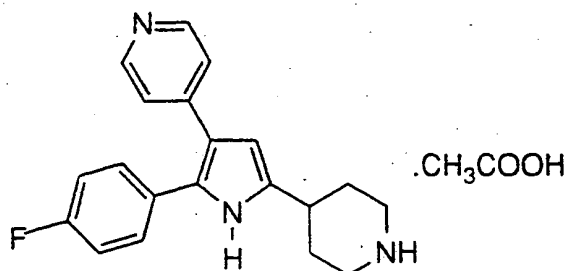


15 2-(4-fluorophenyl)-5-(N-methylpiperidin-4-yl)-3-(4-pyridyl)-pyrrole

To a solution of the product of Example 2 (0.032 g (0.07mmol) in 1 ml of dry THF at room temperature was added 0.14 ml (0.14 mmol) of a 1M solution of lithium aluminum hydride in THF. The reaction mixture was heated at reflux for 2 hours. 3 ml of water
20 was added cautiously and the mixture was extracted with ethyl acetate (3 x 4 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo.

¹H-NMR (CDCl₃, 300 MHz): 1.81 (m, 2H); 1.95-2.12 (m, 4H); 2.30 (s, 3H); 2.59 (m, 1H); 2.95 (bd, 2H); 6.19 (d, 1H); 7.04 (t, 2H); 7.18 (dd, 2H); 7.27-7.38 (m, 4H); 8.39 (dd, 2H). FAB ms: C₂₁H₂₂N₃F:335; Observed: 336 (M⁺+1).
25

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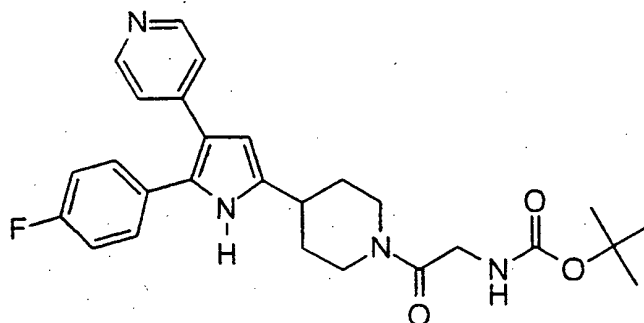
EXAMPLE 45 2-(4-fluorophenyl)-5-(piperidin-4-yl)-3-(4-pyridyl)-pyrrole

183 mg of the product of Example 2 was dissolved in 5 ml of acetic acid. The solution was hydrogenated over 25 hours at atmospheric pressure in the presence of 10 mg of 10% Pd/C. The mixture was filtered and the filtrate was concentrated in vacuo to give the product.

10 FAB ms: C₂₀H₂₀N₃F:321; Observed: 322 (M⁺+1).

EXAMPLE 5

15



15 2-(4-fluorophenyl)-5-(N-(COCH₂NHCO₂-t-butyl)-piperidin-4-yl)-3-(4-pyridyl)-pyrrole

20

To a solution of 35 mg (0.086 mmol) of the product of Example 4 in 5 ml of CH₂Cl₂ at 0°C was added 15 mg (0.086 mmol) of N-Boc glycine, 11.7 mg (0.086 mmol) of N-hydroxybenzotriazole, 9.5 μL (0.086 mmol) of N-methylmorpholine and 24.8 mg (0.12 mmol) of EDC. After stirring overnight at room temperature, the reaction

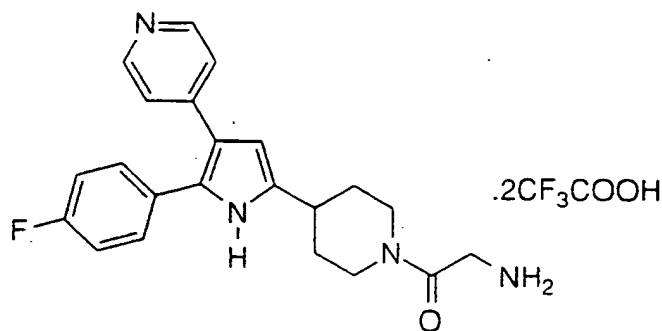
- 61 -

mixture was diluted with water and extracted with ethyl acetate. The combined organic phase was washed with brine and dried over MgSO_4 . The mixture was filtered and concentrated in vacuo and the residue was purified by preparatory TLC eluting with 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$.

5 ^1H -NMR (CDCl_3 , 300 MHz): 1.44 (s, 9H); 1.55-1.70 (m, 2H); 2.08 (m, 2H); 2.71-2.91 (m, 2H); 3.13 (t, 1H); 3.80 (d, 1H); 3.98 (m, 2H); 4.67 (d, 1H); 5.51 (bs, 1H); 6.19 (s, 1H); 7.05 (t, 2H); 7.18-7.31 (m, 4H); 8.08 (s, 1H); 8.41 (d, 2H). FAB ms: $\text{C}_{27}\text{H}_{31}\text{N}_4\text{O}_3\text{F}$:478; Observed:479 (M^++1).

10

EXAMPLE 6



15

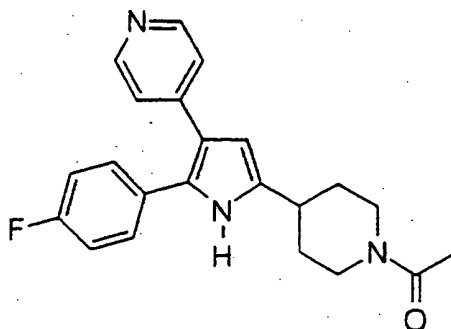
2-(4-fluorophenyl)-5-(N-glycyl)piperidin-4-yl)-3-(4-pyridyl)-pyrrole

9.8 mg of the product prepared in Example 5 was stirred overnight in 50% trifluoroacetic acid in methylene chloride. The reaction mixture was concentrated in vacuo to provide the desired product.

20

FAB ms: $\text{C}_{22}\text{H}_{23}\text{N}_4\text{O}$:378; Observed:379 (M^++1).

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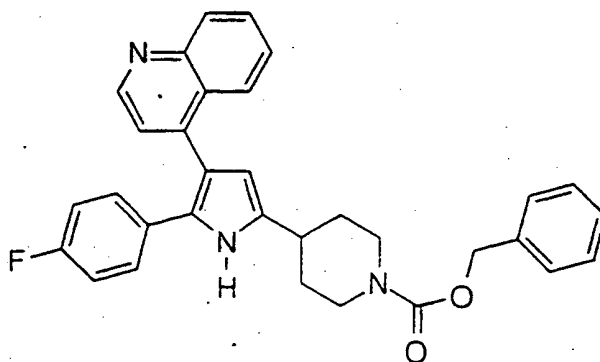
EXAMPLE 75 2-(4-fluorophenyl)-5-(N-acetyl-piperidin-4-yl)-3-(4-pyridyl)-pyrrole

A solution of 10.0 mg of the product of Example 4 was dissolved in 0.5 ml of pyridine and treated with 2.6 μ L of acetic anhydride. The solution was stirred overnight and diluted with 5 ml water and was extracted with ethyl acetate (2 x 5 ml). The combined
10 organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound.

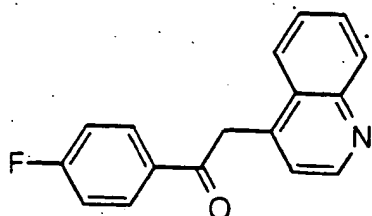
FAB ms: $C_{22}H_{22}N_3OF$:363; Observed: 364 (M^++1).

EXAMPLE 8

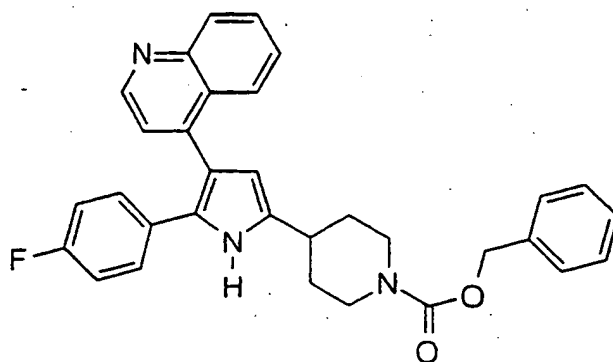
15

2-(4-fluorophenyl)-5-(N-(CBz)-piperidin-4-yl)-3-(4-quinolinyl)-pyrrole

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Step 1

- 5 To a solution of 1.94 g of diisopropylamine in 20 ml of THF at -78°C was added 9.37 g of a 1.6M solution of n-butyl lithium in hexane. After 30 minutes 1.43 g of 4-methylquinoline was added dropwise to give a dark red solution. After 1 hour, 2.26 g of N-methyl-N-methoxy-4-fluorobenzamide in 10 ml of THF was added dropwise.
- 10 The solution was allowed to warm to room temperature over 1.5 hours. The reaction mixture was diluted with 20 ml of water and extracted with ethyl acetate (3 x 15 ml). The combined organic extracts were washed with water (1 x 15 ml) and dried over MgSO_4 . The mixture was filtered and concentrated in vacuo and the residue was purified by
- 15 flash chromatography over silica gel eluting with 2% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ to provide the desired compound.

Step 2

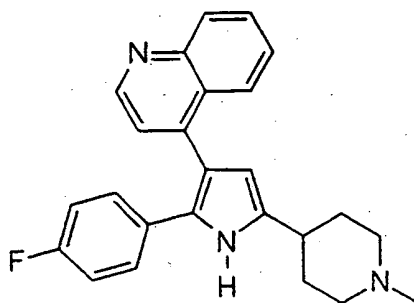
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The procedure described in Example 2, step 4 was followed to give the desired product.

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^1H -NMR (CDCl_3 , 300 MHz): 1.7 (m, 4H); 2.05 (bm, 2H); 2.80-3.05 (m, 3H); 4.30 9bm, 2H); 5.12 (s, 2H); 6.12 (s, 1H); 6.81 (t, 2H); 7.02-7.45 (m, 8H); 7.65 (t, 1H); 8.00 (d, 1H); 8.10 (s, 1H); 8.42 (s, 1H); 8.75 (d, 1H). FAB ms: $\text{C}_{32}\text{H}_{28}\text{N}_3\text{O}_2\text{F}$: 505; Observed: 506 (M^++1).

5

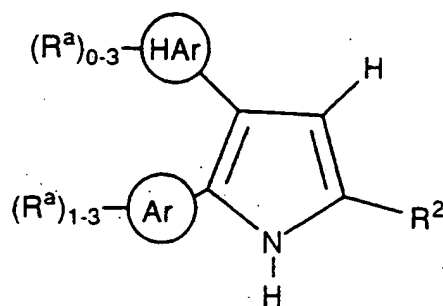
EXAMPLE 910 2-(4-fluorophenyl)-5-(4-methylpiperidin-4-yl)-3-(4-quinolinyl)-pyrrole

The product of Example 8 was converted into the title compound by application of the conditions described for Example 4.

^1H -NMR (CDCl_3 , 300 MHz): 1.90 (m, 2H); 2.02-2.18 (m, 4H); 2.35 (s, 3H); 2.68 (m, 2H); 3.0 (d, 2H); 6.14 (s, 1H); 6.82 (t, 2H); 7.03 (m, 2H); 15 7.19 (d, 1H); 7.38 (m, 2H); 7.64 (t, 1H); 8.02 (d, 1H); 8.09 (d, 1H); 8.30 (bs, 1H); 8.75 (d, 1H). FAB ms: $\text{C}_{25}\text{H}_{24}\text{N}_3\text{F}$: 385; Observed: 386 (M^++1).

Employing the procedures described above, the compounds
20 appearing in the Table below are prepared.

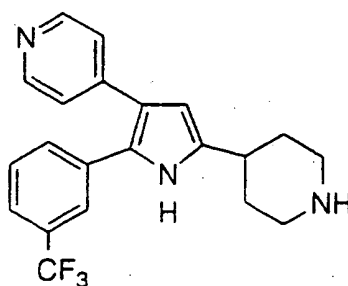
TABLE I



Ex. #	R ²	(R ^a) ₁₋₃ -Ar	(R ^a) ₀₋₃ -HAr
10	t-butyl	Ph-4-F	3-methyl-4-pyridyl
11	t-butyl	Ph-4-F	4-quinolinyl
12	t-butyl	Ph-4-F	2-methyl-4-pyridyl
13	N-Bn-piperidin-4-yl	Ph-4-F	4-pyridyl
14	N-Ph-piperidin-4-yl	Ph-4-F	4-pyridyl
15	N-Me-piperidin-4-yl	Ph-4-Cl	4-pyridyl
16	N-Me-piperidin-4-yl	Ph-3,4-di-F	4-pyridyl
17	N-Me-piperidin-4-yl	Ph-3-Cl	4-pyridyl
18	t-butyl	Ph-2-OMe	4-pyridyl
19	t-butyl	Ph-3-OMe	4-pyridyl
20	t-butyl	Ph-4-OMe	4-pyridyl
21	t-butyl	Ph-4-Cl	4-pyridyl
22	t-butyl	Ph-3-Cl	4-pyridyl
23	t-butyl	Ph-3,4-di-F	4-pyridyl
24	t-butyl	Ph-3,4-di-Cl	4-pyridyl
25	t-butyl	Ph-3-CF ₃	4-pyridyl
26	t-butyl	Ph-4-SMe	4-pyridyl
27	t-butyl	Ph-4-S(O)Me	4-pyridyl

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28	4-piperidinyl	Ph-4-F	4-pyridyl
29	N-Me-piperidin-3-yl	Ph-4-F	4-pyridyl
30	t-butyl	Ph-4-NO ₂	4-pyridyl
31	t-butyl	Ph-4-NMe ₂	4-pyridyl
32	t-butyl	Ph-2-Cl	4-pyridyl
33	N-Me-piperidin-4-yl	Ph-3-CF ₃	4-quinolinyl
34	4-piperidinyl	Ph-3-CF ₃	4-quinolinyl
35	N-CBz-piperidin-4-yl	Ph-2-CF ₃	4-(2-F)-pyridyl
36	N-methylpiperidin-4-yl	Ph-4-F	2-methylpyridin-4-yl
37	N-methylpiperidin-4-yl	Ph-3-CF ₃	2-methylpyridin-4-yl
Me = methyl, CBz = benzyloxycarbonyl Bn = benzyl Ph = phenyl Boc = butoxycarbonyl			

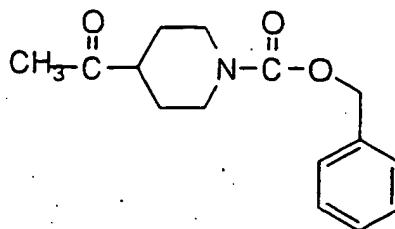
EXAMPLE 38

5

2-(3-trifluoromethylphenyl)-5-(4-piperidyl)-3-(4-pyridinyl)-pyrroleStep 1: 4-acetyl-1-(benzyloxycarbonyl)piperidine

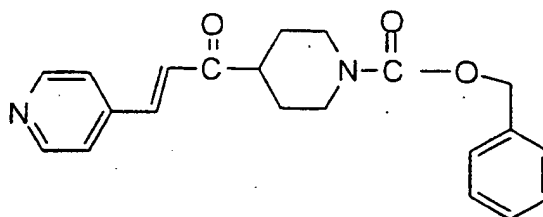
10

- 67 -



- To a stirred solution of 4-acetypiperidine hydrochloride (22.6 g, 0.138 mol) in saturated aqueous Na₂CO₃ (100 mL), cooled to 5°C, was added benzyl chloroformate (23.6 mL, 0.166 mol) dropwise over 10 - 15 min. The resulting suspension was stirred for 1/2 hour and was filtered. The solid was recrystallized from hexane (200 mL) and ethyl acetate (20 mL) producing 30.5 g of the title compound as a white solid.
- 10 M.P. 87-89°C.

Step 2: 1-(1-benzyloxycarbonyl-4-piperidinyl)-3-(4-pyridinyl)-2-propen-1-one

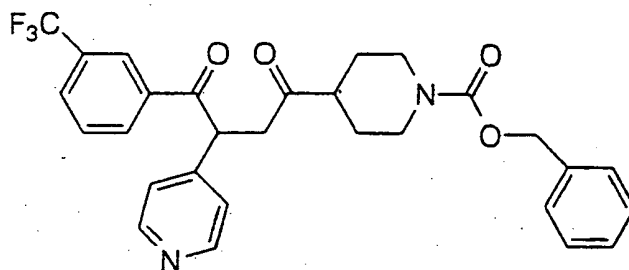


15

- To a solution of 4-pyridinecarboxaldehyde (5.89 g, 0.055 mol), 4-acetyl-1-(N-benzyloxycarbonyl)piperidine (13.07 g, 0.05 mol) and piperidine (4.26 g, 0.005 mol) was added 15 mL of pyridine. The mixture was stirred in an oil bath at 100 °C for 20 hours, and the volatile components were removed in vacuo. The residual oil was chromatographed on silica gel, eluting with ethyl acetate to produce the title compound (3.78 g) as a colorless oil, which formed a pale yellow solid.
- 20
- 25 M. P. 106-112°C.

Step 3: 4-(1-benzyloxycarbonylpiperidin-4-yl)-2-(4-pyridyl)-1-

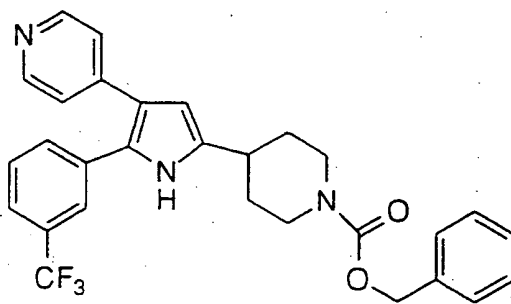
- 68 -

(3-trifluoromethylphenyl)butane-1,4-dione

5 To m-trifluoromethylbenzaldehyde (2.44 g, 0.014 mol) in 5 mL of DMF was added NaCN (0.147 g, 0.003 mol) and the mixture was stirred under argon for 1 hour. This solution was added to 1-(1-benzyloxycarbonyl-4-piperidiny)-3-(4-pyridyl)-2-propen-1-one in 10 mL of DMF. The mixture was stirred at 65-75 °C for 20 hours. The volatile components were removed in vacuo. The residual oil was taken up in EtOAc and sat'd NaCl. The EtOAc extract was separated, dried, filtered and concentrated in vacuo to form an oil. The crude oil was chromatographed on silica gel eluting with ethyl acetate, producing 3.45 g of the title compound as a yellow foam.

15

Step 4: 5-(1-benzyloxycarbonyl-4-piperidiny)-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)-pyrrole



20

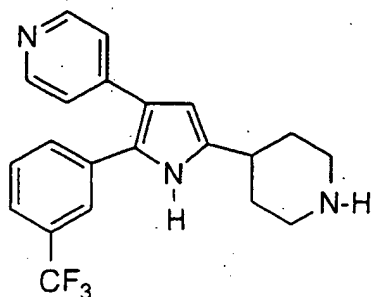
The 1,4-diketone from step 3 (3.45 g, 6.6 mmol) was reacted with ammonium acetate (20.3 g, 0.264 mol) and 50 mL of acetic acid using the procedure of Example 1, step 3, producing 3.28 g of the title compound.

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M. P. 180-181°C.

Step 5: 3-(4-pyridyl)-5-(4-piperidiny)-2-(3-trifluoromethyl-phenyl) pyrrole

5

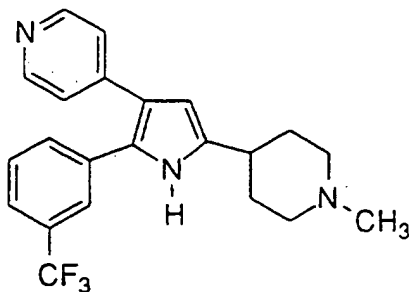


The product from step 4 (3.0 g, 0.006 mol) was debenzylated in 5 mL of 30% HBr in acetic acid and 5 mL of methylene chloride, producing the title compound as a solid.

M. P. 238-240°C.

10

EXAMPLE 39



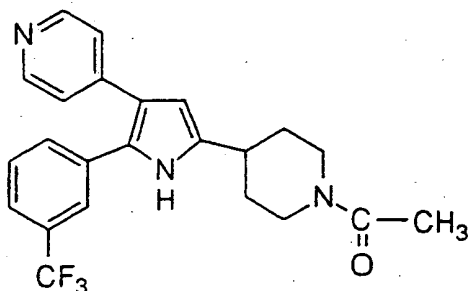
15

The product from Example 38, Step 4 (1.15 g, 2.27 mmol) was reduced with lithium aluminum hydride (0.86 g, 2.27 mmol) using the procedure of Example 3. The N-methylpiperidiny analog was obtained.

M. P. 221-222°C.

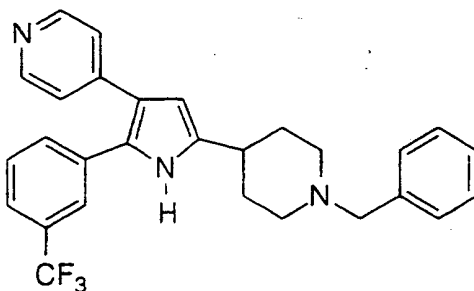
20

- 70 -

EXAMPLE 40

5 The N-acetylpiperidinyl analog was prepared from the product of Example 38 was prepared using acetyl chloride and triethylamine in THF in place of acetic anhydride and pyridine, as described in Example 7, producing the target compound as a solid. M. P. 196-198°C.

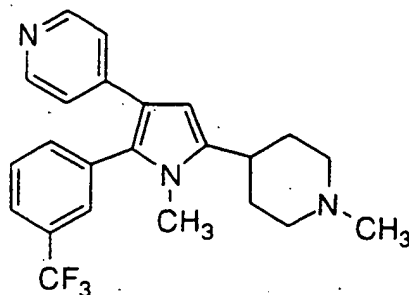
10

EXAMPLE 41

15 The product of Example 38 (111 mg, 0.3 mmol) was reacted with benzaldehyde (35 mg, 0.33 mmol) in a reductive amination using sodium triacetoxyborohydride (95 mg, 0.45 mmol) in 3 mL of 1,2-dichloroethane and 2 mL of THF, producing the target compound as a solid.

20 M. P. 212-214°C.

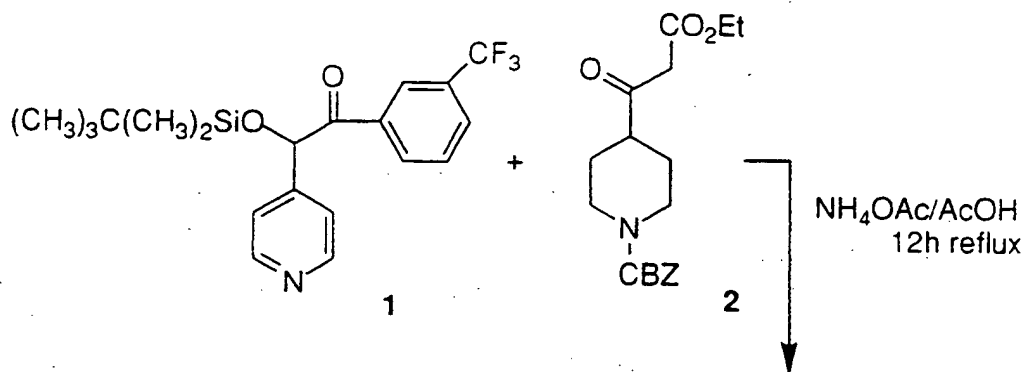
- 71 -

EXAMPLE 42

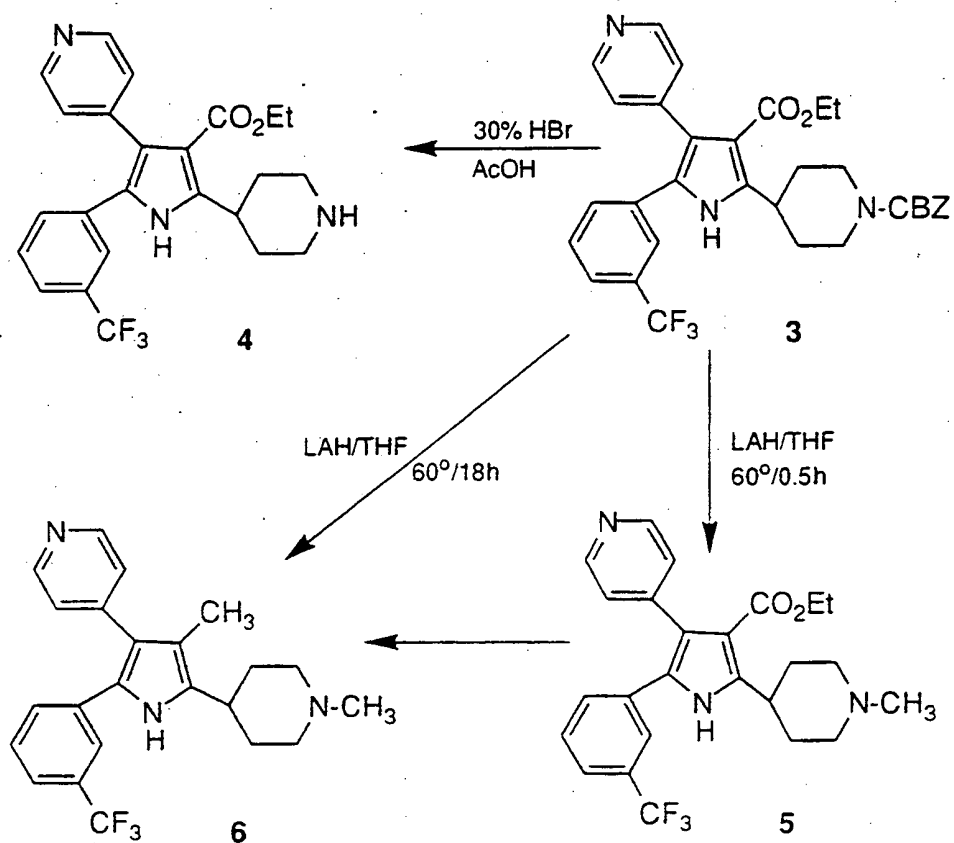
- 5 Powdered KOH (78 mg, 1.39 mmol) was stirred in 1 mL of DMSO for 5 min. The product of Example 54 (134 mg, 0.348 mmol) was added and the mixture was stirred for 3/4 hour. Methyl iodide (49 mg, 0.348 mmol) was added and the solution was stirred for 1 1/4 hours at room temperature. Another 49 mg of methyl iodide was added. After 1/2 hour, 10 mL of water was added and the mixture was
- 10 extracted with ethyl acetate. The crude product isolated from ethyl acetate was chromatographed on silica gel, eluting with 20% methanol-chloroform, to produce the target compound as a solid.

EXAMPLE 43

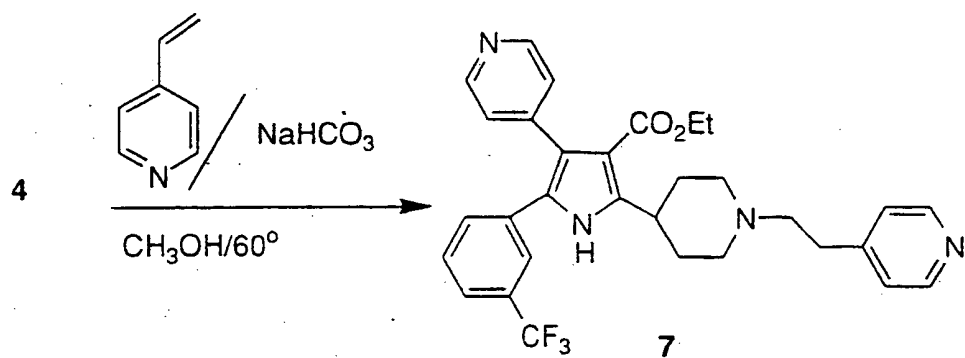
15



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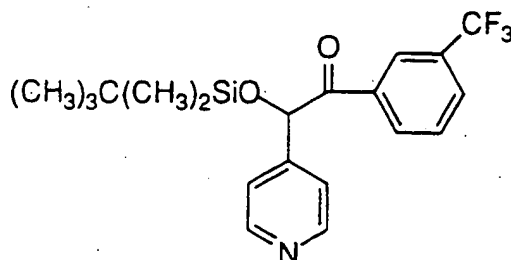


CBZ = carboxybenzyl



5 Preparation of 3-trifluoromethyl-2-(4-pyridyl)-2-tert butyldimethylsilyloxyacetophenone (I)

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To a 2 liter 3-neck flask equipped with a mechanical stirrer under N₂ was added 54.6 g (0.59 m) of diisopropylethylamine and 150 mL of THF. The solution was cooled to -20°C and treated with 268 mL (0.67m) of 2.5 M n-butyl lithium over 20 min. To the reaction mixture was added 125 g (0.56 m) of 4-(t-butyl dimethylsilyloxymethyl) pyridine in 100 mL of THF over 30 min. The reaction mixture was stirred for 1 hr. at -15°C and then treated dropwise with a solution of 108 g (0.59 m) of 3-trifluoromethylbenzaldehyde dissolved in 100 mL of THF. The reaction was warmed to 0°C, stirred for 1 hr, warmed to room temperature and then quenched by the addition of 1 L of 20% NH₄Cl solution. The aqueous phase was extracted with EtOAc (3 x 500 mL).

15 The combined organic phases were washed with water (1 x 500 mL), 1 x 500 mL brine and then dried over MgSO_4 . The mixture was filtered and the filtrate was concentrated in vacuo to give a dark oil. The product was purified by flash chromatography over silica gel eluting with 10-20% EtOAc/hexanes.

20 Preparation of 5-[(N-benzyloxycarbonyl)piperidin-4-yl]-4-carboethoxy-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (3)

25 A mixture of compound 2, prepared in accordance with J. Med. Chem. Vol. 38, p. 3293 (1995), 0.7 equivalents of the product of Step 1, and 4 equivalents of ammonium acetate are heated in acetic acid at reflux. The reaction mixture is diluted with ethyl acetate, washed with water and brine, and dried over MgSO_4 . The mixture is filtered and then concentrated in vacuo, and the residue is purified by chromatography over silica gel to give the desired product.

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Preparation of 5-[piperidin-4-yl]-4-carboethoxy-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (4)

A mixture of 3 (0.4g, 0.69mmol) and 4 mL of 30% HBr in AcOH was stirred under N₂ for 1 hour. The mixture was then treated with EtOAc-Et₂O-1N HCl and the phases were separated. The aqueous layer was extracted with EtOAc, neutralized with saturated NaHCO₃ and extracted with EtOAc (3x). The organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a column (40mm) and the product eluted with 5% CH₃OH-CHCl₃ saturated with ammonia. M.P. 233-5°C (EtOAc-Hexanes).

Analysis calculated for C₂₄H₂₄F₃N₃O₂ • 0.5 H₂O:

C, 63.70; H, 5.57; N, 9.29

Found: C, 63.98; H, 5.46; N, 9.20.

¹H NMR (CDCl₃ 300 MHz) 1.0 (t, 3H); 1.85 (m, 5H); 2.8 (t, 2H); 3.2 (d, 2H) 3.7(t, 1H); 4.1(q, 2H); 7.16 (d, 3H); 7.3 (t, 1H), 7.4(s, 1H); 7.46 (d, 1H); 8.52 (d, 2H); and 8.94 (bs. exch 1H).

Preparation of 5-[N-methylpiperidin-4-yl]-4-carboethoxy-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (5)

Under Ar, a solution of 3 in THF (70 ml) was treated at room temperature with 1N LAH (30ml, 30mmol) and then heated to 60°C. After 0.5 h, the reaction mixture was cooled to room temperature and treated with saturated Na₂SO₄. The suspension was filtered and the precipitate washed with EtOAc. Water was added to the filtrate, the liquid phases separated and the aqueous fraction was extracted with 2 additional EtOAc washes. The combined organic extracts were washed with brine, dried, filtered and concentrated to dryness. The residue was chromatographed on a column (40 mm) and the product eluted with 10% CH₃OH-CHCl₃ saturated with ammonia. M.P. 223-5°C (EtOAc-Hexanes).

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Analysis calculated for $C_{25}H_{26}F_3N_3O_2 \cdot 0.25H_2O$:

C, 64.99; H, 5.78; N, 9.10

Found: C, 65.08; H, 5.70; N, 9.06.

- 5 1H NMR ($CDCl_3$ 300 MHz) 1.0 (t, 3H); 1.8 (m, 2H); 2.1 (m, 4H); 2.15 (s, 3H); 3.0 (d, 2H); 3.6 (m, 1H); 4.05 (q, 2H); 7.16 (d, 3H); 7.3 (t, 1H); 7.38 (s, 1H); 7.45 (d, 1H); 8.55 (d, 2H); 8.81 (bs, 1H).

- 10 Preparation of 5-(N-methylpiperidin-4-yl)-4-methyl-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (6)

Using the procedure described for the preparation of 5 and refluxing the mixture overnight provided 6.

M.P. 245-7°C (CH_2Cl_2 -Hexanes).

- 15 Analysis calculated for: $C_{23}H_{24}F_3N_3$:
C, 69.15; H, 6.06; N, 10.52
Found: C, 68.78; H, 5.97; N, 10.56.

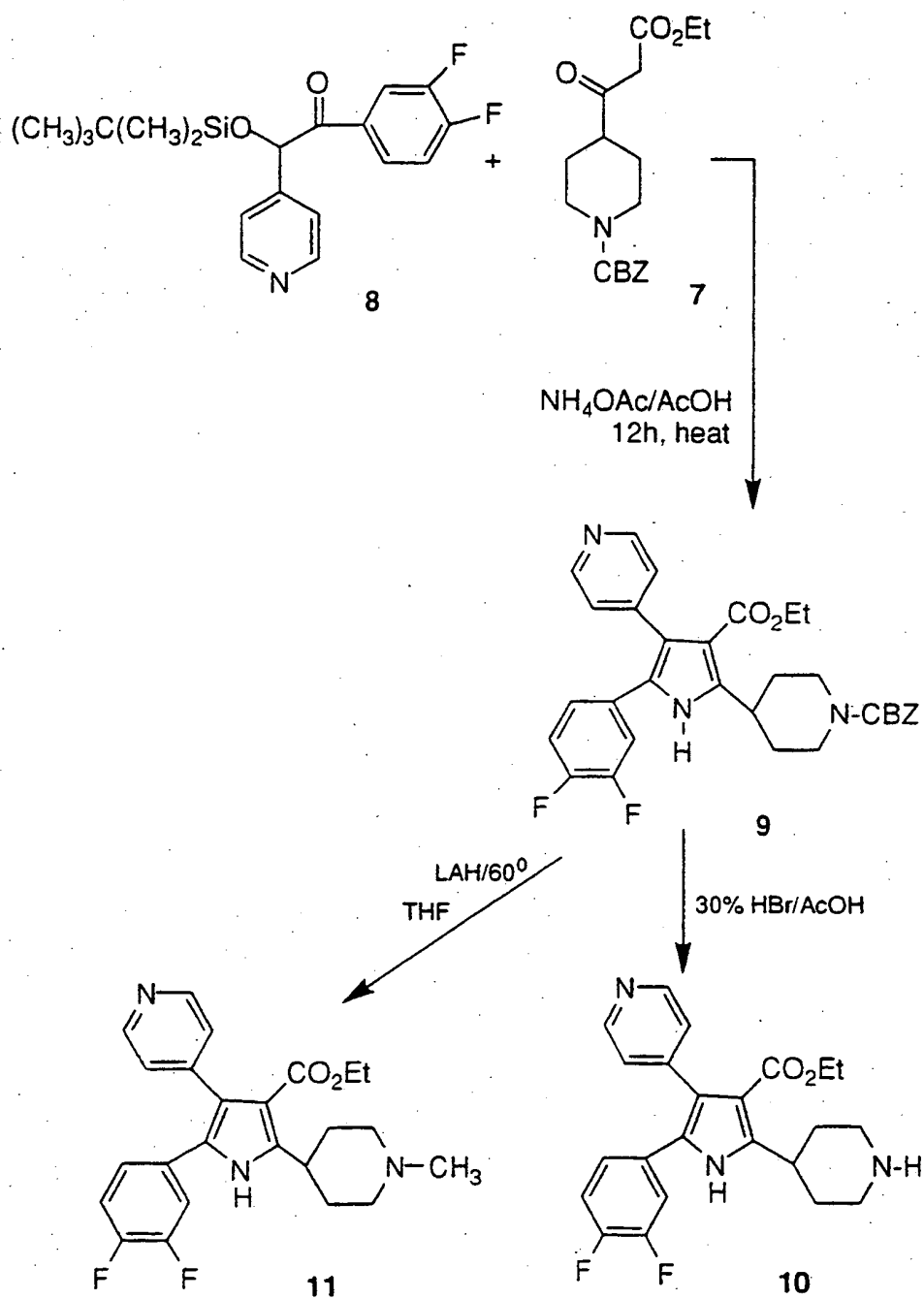
- 20 Preparation of 5-[N-(2-ethylpyridin-4-yl) piperidin-4-yl]-4-carboethoxy-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (7)

- Under Ar, a mixture of 4 (0.25 g, 0.56 mmol), $NaHCO_3$ (100 mg, 1.2 mmol), CH_3OH (5 ml) and 4-vinylpyridine (0.47 g, 4.6 mmol) was heated at reflux. After 18 hours, the reaction was poured into a saturated $NaHCO_3$ solution and extracted with EtOAc (3 x). The
25 organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a column (40 mm) and the product eluted with $CHCl_3$ saturated with NH_3 .

M.P. 176-7°C (EtOAc-Hexanes).

- 30 Analysis calculated for $C_{31}H_{31}F_3N_4O_2$:
C, 67.87; H, 5.70; N, 10.21
Found: C, 67.67; H, 5.60; N, 10.21.

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EXAMPLE 44

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Preparation of 3,4-difluoro-2-(4-pyridyl)-2-tert butyldimethylsilyl-
oxyacetophenone (8)

Using the procedure described in Example 43, Step 1,
compound 8 was prepared by substituting 3,4-difluoro-(N-methyl-N-
5 methoxy)benzamide in place of 4-fluoro-(N-methyl-N-methoxy)
benzamide.

Preparation of 5-[(N-benzyloxycarbonyl)piperidin-4-yl]-4-carboethoxy-
3-(4-pyridyl)-2-(3,4-difluoromethylphenyl)pyrrole (9)

10 Using the procedure described in Example 43, Step 2,
compound 9 was prepared.

Preparation of 5-(piperidin-4-yl)-4-carboethoxy-3-(4-pyridyl)-2-(3,
4-difluorophenyl)pyrrole (10)

15 Using the procedure described in Example 43 to prepare 4,
compound 10 was prepared.
M.P. 261-2°C (EtOAc).

Analysis calculated for $C_{23}H_{23}F_2N_3O_2 \cdot 0.5 H_2O$:

20 C, 65.70; H, 5.75; N, 9.99

Found: C, 65.97; H, 5.51; N, 9.88.

1H NMR (DMSO- d_6 300MHz) 0.95 (t, 3H); 1.75 (m, 4H); 2.5 (m, 4H);
3.05 (d, 2H); 3.5 (m, 1H); 3.95 (q, 2H); 6.9 (d, 1H); 7.15 (d, 2H); 7.3
25 (m, 3H); 8.45 (d, 2H); 11.5 (bs, 1H).

Preparation of 5-[N-methylpiperidin-4-yl]-4-carboethoxy-3-(4-pyridyl)-
2-(3,4-difluorophenyl)pyrrole (11)

30 Using the procedure described in Example 43 to prepare 5,
the title compound 11 was prepared.
M.P. 262-5°C (EtOAc).

Analysis calculated for $C_{24}H_{25}F_2N_3O_2$:

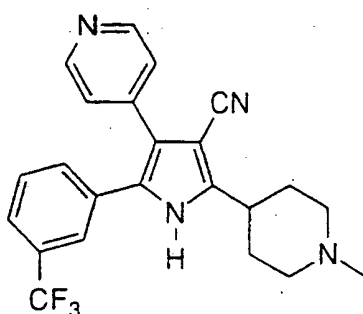
C, 67.75; H, 5.92; N, 9.88

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Found: C, 67.61; H, 5.92; N, 9.67.

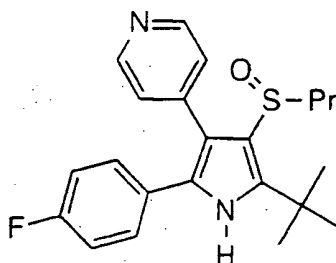
¹NMR (CDCl₃ 300 MHz) 1.0 (t, 3H); 1.8 (m, 2H); 2.1 (m, 4H); 2.35 (s, 3H); 3.0 (d, 2H); 3.6 (m, 1H); 4.05 (q, 2H); 7.16 (d, 3H); 7.31 (t, 1H);
5 7.38 (s, 1H); 7.45 (d, 1H); 8.51 (d, 2H); and 8.82 (bs, 1H).

EXAMPLE 45



A mixture of 1-(4-N-methylpiperidinyl)-2-cyanoethanone,
10 0.7 equivalents of the reaction product of Example 43, Step 1, and 4
equivalents of ammonium acetate are heated in acetic acid at reflux until
the benzoin is consumed. The reaction mixture is diluted with EtOAc
and washed with water and brine and dried over MgSO₄. The mixture
is filtered and the filtrate is concentrated in vacuo. The residue is
15 purified by chromatography over silica gel to give the desired product.

EXAMPLE 46

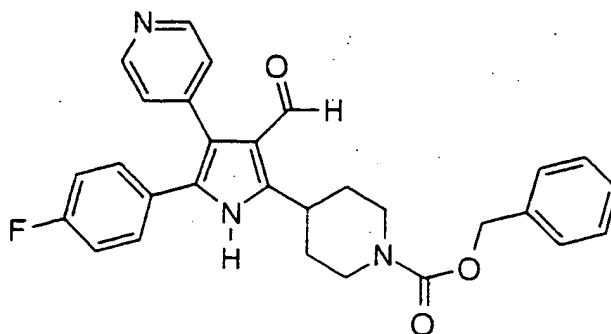


The product of Example 1 is dissolved in methylene
20 chloride and treated with 1.05 equivalents of n-propylsulfinyl chloride
at 0°C under nitrogen. After 30 minutes triethylamine is added to

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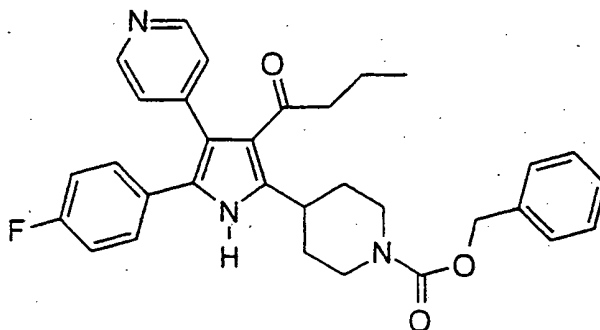
neutralize the reaction mixture. The reaction mixture is diluted with ethyl acetate and washed with water and brine and dried over MgSO_4 . The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 47

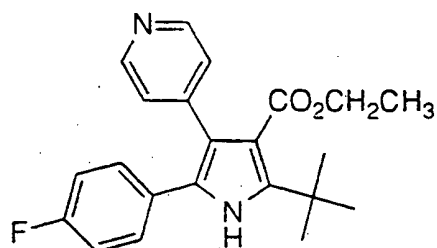


To 5 ml of DMF at room temperature under nitrogen is added 0.3 g (2 mmol) of POCl_3 dropwise. After 15 minutes a solution of 0.37 g (0.86 mmol) of the product of Example 2 is added dropwise. The solution was warmed at 60°C until the starting material had been consumed. The reaction mixture was cooled to room temperature and then poured into ice water (20 ml). The mixture was made basic by addition of saturated sodium carbonate solution and then stirred in the presence of 20 mL of chloroform. The chloroform phase was separated and the aqueous phase was extracted with chloroform (2 x 10 mL). The combined organic phase is washed with water and brine and dried over MgSO_4 . The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

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EXAMPLE 48

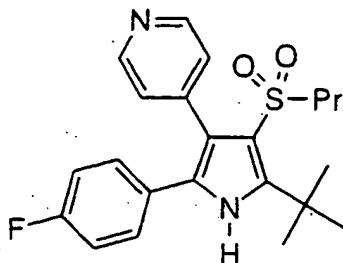
To 5 ml of N,N-dimethylbutyramide at room temperature under nitrogen is added 0.3 g (2 mmol) of POCl₃ dropwise. After 15 minutes a solution of 0.37 g (0.86 mmol) of the product of Example 2 is added dropwise. The solution is warmed at 60°C until the starting material had been consumed. The reaction mixture is cooled to room temperature and then poured into ice water (20 ml). The mixture is made basic by addition of saturated sodium carbonate solution and then stirred in the presence of 20 mL of chloroform. The chloroform phase is separated and the aqueous phase extracted with chloroform (2 x 10 ml). The combined organic phase is washed with water and brine and dried over MgSO₄. The mixture is filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 49

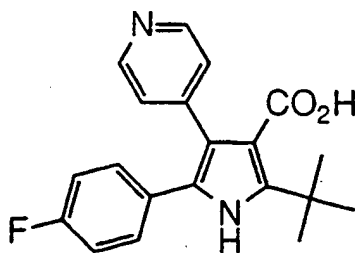
20

Using the procedure set forth in Example 43, substitute EtO₂CCH₂C(O)C(CH₃)₃ for compound 2 to produce the desired compound.

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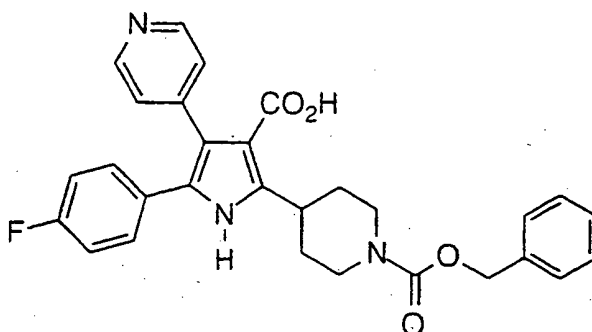
EXAMPLE 50

The product of Example 1 is reacted with 1.05 equivalents
5 of meta-chloroperoxybenzoic acid in CH_2Cl_2 at 0°C . The reaction
mixture is stirred overnight at room temperature. The solution is
diluted with EtOAc and washed with saturated sodium bicarbonate
solution followed by brine. The solution is dried over MgSO_4 , filtered
and concentrated in vacuo. The residue is purified by silica gel
10 chromatography to produce the desired product.

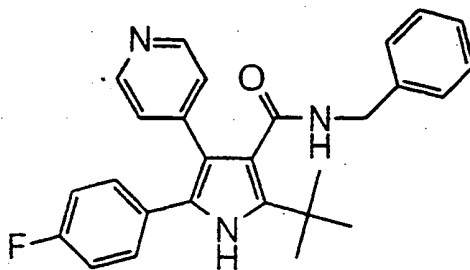
EXAMPLE 51

The product of Example 49 is heated with excess lithium
15 hydroxide in DME/water at reflux until the conversion to the acid is
complete. The reaction mixture is acidified with acetic acid and
extracted with ethyl acetate to give the desired product.

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EXAMPLE 52

The product of Example 47 is dissolved in t-butyl alcohol and methyl 2-butene (6:1 ratio). The solution is then treated with 1.5 eq of monobasic sodium phosphate and an aqueous solution of sodium chlorate. The reaction mixture is stirred at room temperature until the starting material is consumed. The pH is adjusted to 5.5 with dilute HCl. The product is extracted with ethyl acetate and the combined organic phase is washed with water and brine and dried over MgSO₄. The mixture is filtered and the filtrate is concentrated in vacuo to give the desired product.

EXAMPLE 53

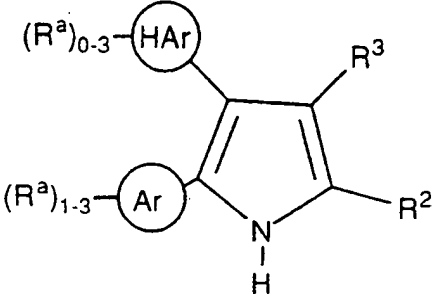
The product of Example 51 is dissolved in DMF and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, benzylamine, Hunig's base and a catalytic amount of DMAP. The mixture is stirred overnight at room temperature. The solution is diluted with water and extracted with ethyl acetate. The organic phase is

washed with water and brine and is dried over MgSO_4 , filtered and concentrated in vacuo. The residue is purified by chromatography.

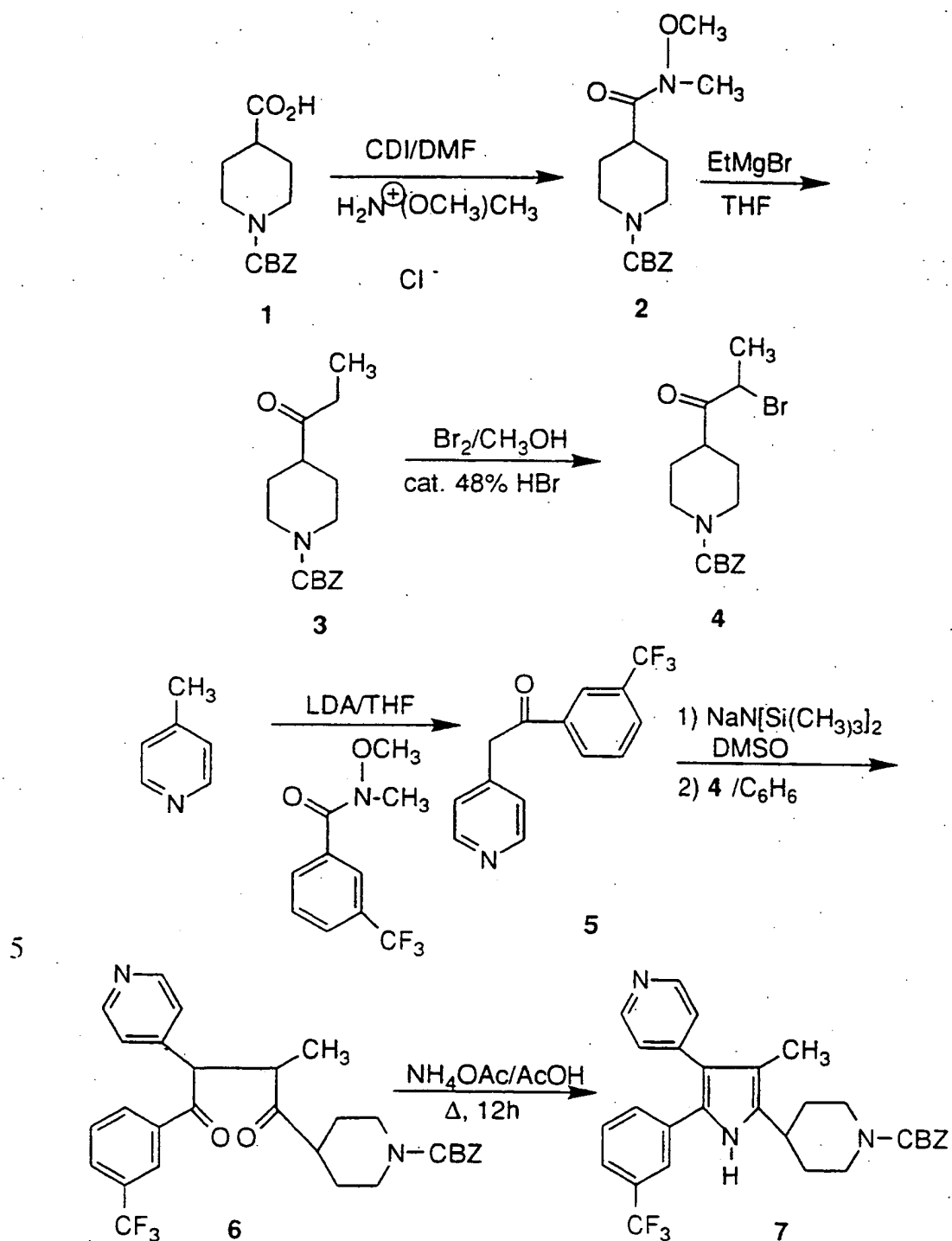
EXAMPLES 54-109

5.

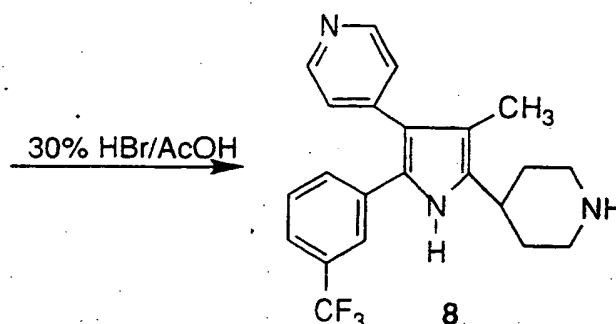
Employing the procedures described above, the following compounds of Formula I can be prepared.

TABLE II				
				
Ex. #	R^2	$(\text{R}^a)_{1-3}-\text{Ar}$	$(\text{R}^a)_{0-3}-\text{HAr}$	R^3
54	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CN
55	t-butyl	Ph-4-F	2-methyl-4-pyridyl	COMe
56	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CONHMe
57	t-butyl	Ph-4-F	2-methyl-4-pyridyl	SO_2Et
58	t-butyl	Ph-4-F	2-methyl-4-pyridyl	COOEt
59	t-butyl	Ph-4-F	4-quinoliny	CN
60	t-butyl	Ph-4-F	2-quinoliny	CN
61	t-butyl	Ph-4-F	2-pyrimidiny	CN
62	t-butyl	Ph-4-F	4-pyrimidiny	CN
63	t-butyl	Ph-4-F	3-pyridaziny	CN
64	t-butyl	Ph-4-F	2-pyraziny	CN
65	t-butyl	Ph-4-F	2-pyrimidiny	CN
66	t-butyl	Ph-4-F	4-pyrimidiny	CN
67	t-butyl	Ph-4-F	2-imidazo-(4,5-b)-pyridiny	CN
68	t-butyl	Ph-4-F	4-(2-amino)-pyridyl	CN
69	t-butyl	Ph-4-F	4-(2-N-benzyl-amino)-pyridyl	CN
70	t-butyl	Ph-4-F	4-(2-acetylamino)-pyridyl	COMe
71	t-butyl	Ph-4-F	4-pyridyl	CN

72	t-butyl	Ph-4-F	4-pyridyl	CONH-iBu
73	t-butyl	Ph-4-F	4-pyridyl	COMe
74	i-butyl	Ph-4-F	4-pyridyl	CN
75	N-Me-piperidin-4-yl	Ph-4-F	4-pyridyl	COMe
76	N-Bn-piperidin-4-yl	Ph-4-F	4-pyridyl	COMe
77	N-Ph-piperidin-4-yl	Ph-4-F	4-pyridyl	COMe
78	CH ₂ -4-(N-Me)-piperazinyl	Ph-4-F	4-pyridyl	CN
79	N-Me-piperidin-4-yl	Ph-4-F	4-pyridyl	CN
80	N-Me-piperidin-4-yl	Ph-4-Cl	4-pyridyl	CN
81	t-butyl	Ph-2-OMe	4-pyridyl	CN
82	t-butyl	Ph-3-OMe	4-pyridyl	CN
83	t-butyl	Ph-4-OMe	4-pyridyl	CN
84	t-butyl	4-(4-(N-COCH ₃)-piperazinyl)-Ph	4-pyridyl	CN
85	t-butyl	4-(morpholinyl)-Ph	4-pyridyl	CN
86	t-butyl	Ph-4-Cl	4-pyridyl	CN
87	t-butyl	Ph-3-Cl	4-pyridyl	CN
88	t-butyl	Ph-3,4-di-Cl	4-pyridyl	CN
89	t-butyl	Ph-3-CF ₃	4-pyridyl	CN
90	t-butyl	Ph-4-S-Me	4-pyridyl	CN
91	t-butyl	Ph-4-S(O)-Me	4-pyridyl	CN
92	4-piperidinyl	Ph-4-F	4-pyridyl	CN
93	3-N-Me-piperidinyl	Ph-4-F	4-pyridyl	CN
94	CH ₂ -morpholin-1-yl	Ph-4-F	4-pyridyl	CN
95	t-butyl	Ph-4-NO ₂	4-pyridyl	CN
96	t-butyl	Ph-4-NMe ₂	4-pyridyl	CN
97	t-butyl	Ph-2-Cl	4-pyridyl	CN
98	4-piperidinyl	Ph-4-F	4-pyridyl	CN
99	t-butyl	Ph-4-F	2-pyridyl	CN
100	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CN
101	t-butyl	Ph-4-F	3-methyl-4-pyridyl	CN
102	cyclohexyl	Ph-4-F	4-pyridyl	CN
103	i-propyl	Ph-4-F	4-pyridyl	CN
104	1-cyclopropyl-ethyl	Ph-4-F	4-pyridyl	CN
105	t-butyl	Ph-4-F	2,4-dimethylpyridin-4-yl	CN
106	4-(N-Cbz)-piperidinyl	Ph-4-F	4-pyridyl	H
107	4-(N-Cbz)-piperidinyl	Ph-4-F	4-quinolinyl	H
108	4-(N-Cbz)-piperidinyl	3-(CF ₃)-Ph	4-(2-F)-pyridyl	
109	t-butyl	Ph-4-F	2,6-dimethylpyridyl	CN

EXAMPLE 110

- 86 -



Preparation of N-benzyloxycarbonylpiperidin-4-(N-methyl-N-methoxy)carboxamide (2)

- 5 To a solution of 1 (6.6 g, 0.025 mol) in DMF (20 ml) stirred at room temperature under N_2 was added carbonyldiimidazole (6.8 g, 0.042 mol). After stirring for 0.5 h, N,O-dimethylhydroxylamine $\cdot \text{HCl}$ (4.4 g, 0.045 mol) was added. After stirring overnight at room temperature, the reaction mixture was poured in 1.5 N HCl and
- 10 then extracted with EtOAc (3x). The organic extracts were backwashed with saturated NaHCO_3 , dried, filtered and concentrated to dryness. The residue was chromatographed on a column (90 mm) and the product eluted with 50-60% EtOAc-Hexanes to yield 2.

15 Preparation of 3-(N-benzyloxycarbonylpiperidin-4-yl)-3-oxopropane (3)

- To a cooled solution at -10°C of 2 (4.0g, 13 mmol) in THF (75 ml) was added dropwise under N_2 a solution of 3M ethylmagnesium bromide in Et_2O (11 ml, 33 mmol). After addition, the ice
- 20 bath was removed and allowed to stir to room temperature. After 0.5 h, the reaction was poured into 3 N HCl and the aqueous mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, saturated NaHCO_3 , dried, filtered and concentrated to dryness to yield 3.6 g of 3.

25

Preparation of 2-bromo-3-(N-benzyloxycarbonylpiperidin-4-yl)-3-oxopropane (4)

To a solution of 3 (3.3 g, 11.6 mmol) in CH₃OH (50 ml) under Ar with 48% HBr (100 μ L) was added dropwise at room temperature bromine (1.9 g, 11.8 mmol). After stirring overnight, the solution was poured in saturated NaHCO₃ and the aqueous solution
5 extracted with EtOAc (3x). The combined organic extracts were backwashed with brine, dried, filtered and concentrated to dryness to yield 4.3g of 4.

Preparation of 3-trifluoromethyl-2-(4-pyridyl)acetophenone (5)

10 Under Ar, a solution of diisopropylamine (9.5 g, 0.094 mol) in THF (100 mL) was cooled to -78°C and 38 mL of 2.5 M n-Bu Li in hexane (0.094 mol) was added dropwise. After 10 min at -78°C, 4-picoline (5.9 g, 0.064 mol) was added.

The solution was stirred for 15 min at -78°C and then 3-
15 trifluoromethyl-(N-methyl-N-methoxy)benzamide (15 g, 0.064 mol) in THF (60 mL) was added dropwise at -78°C. After 15 min, the reaction was allowed to stir at room temperature. After 3 hours, the reaction was poured into saturated NH₄Cl and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried, filtered and
20 concentrated to dryness to yield 17g of the title compound 5.

Preparation of 5-[(N-benzyloxycarbonyl)piperidin-4-yl]-4-methyl-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (7)

To a solution of 5 (1.5 g, 5.7 mmol) in DMSO (10 mL) was
25 added under Ar at room temperature 1.0 M sodium bistrimethylsilylamide in THF (6 mmol). After 0.5 hours, a solution of 4 (2.0 g, 5.6 mmol) in DMSO (5 mL) was added dropwise. After 5.5 hours, 2N AcOH (50 mL) was added and the resulting solution extracted with EtOAc (3 x). The combined organic extracts were washed with water.
30 brine, dried, filtered and concentrated to dryness to yield crude 6. The residue was treated with NH₄OAc (3.0 g, 39 mmol) and acetic acid (25 mL) and heated to reflux. After 12 hours, the reaction was poured into H₂O and extracted with EtOAc (3x). The combined organic extracts were backwashed with H₂O, saturated Na₂CO₃, dried, filtered and
35 concentrated to dryness. The residue was chromatographed on a

column (60 mm) and the product eluted with 30-50% EtOAc/Hexanes to yield 370 mg of compound 7.

5 Preparation of 5-(piperidin-4-yl)-4-methyl-3-(4-pyridyl)-2-(3-trifluoromethylphenyl)pyrrole (8)

Under Ar, a mixture of 7 (370 mg, 0.7 mmol) in 30% HBr - acetic acid (4 mL) was stirred at room temperature. After 1 hour, the reaction was partitioned between 2N HCl - EtOAc. The aqueous layer was poured into saturated Na₂CO₃ and extracted with EtOAc (3 x). The
10 combined organic extracts were dried, filtered and concentrated to dryness to yield 79 mg of compound 8.
M.P. 239 -241°C (EtOAc).

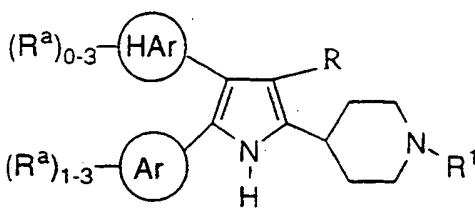
¹H NMR (DMSO 300 MHz) 1.8 (m, 4H); 2.0 (s, 3H); 2.8 (m, 3H); 3.2
15 (d, 2H); 3.35 (bs, exch); 7.15 (d, 2h); 7.45 (m, 4h); 8.45 (d, 2h), 11.0 (br, 1 exch).

Analysis calculated for C₂₂H₂₂F₃N₃• 2.25 H₂O:

C, 62.03; H, 6.27; N, 9.87.

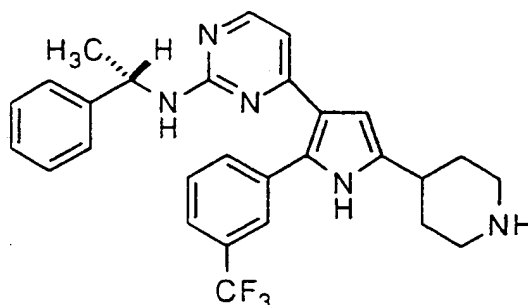
20 Found: C, 62.08; H, 5.60; N, 9.66.

Utilizing the procedures described in the preceeding examples, the following compounds were prepared.

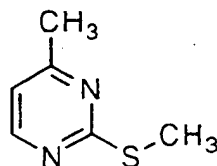
						
Ex.	(R ^a) ₁₋₃ -Ar	(R ^a) ₀₋₃ -HAr	R	R ¹	M.P.°C	Solvent

- 89 -

111	3,4-di-F-C ₆ H ₃	4-C ₅ H ₄ N	CH ₃	CH ₃	>300	MeOH/ EtOAc
112	3-CF ₃ -C ₆ H ₄	4-C ₅ H ₄ N	Ethyl	CH ₃	229-31	-
113	3,4-di-Cl- C ₆ H ₄	4-C ₅ H ₄ N	CH ₃	CH ₃		triturate Hxns
114	3,4-di-Cl- C ₆ H ₄	4-C ₅ H ₄ N	CH ₃	H		EtOAc/ Hxns
115	3-CF ₃ -C ₆ H ₄	4-C ₅ H ₄ N	CH ₃	SO ₂ C ₆ H ₅	237-9	EtOAc/ Hxns

EXAMPLE 116

5

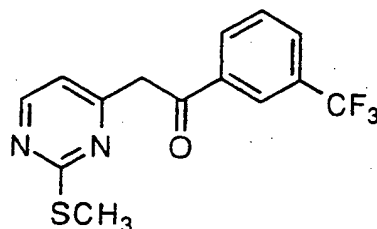
Step 1

- 10 2-Mercapto-4-methylpyrimidine hydrochloride (100g, 0.617 mol), dimethylformamide dimethylacetal (100 mL, 0.754), diisopropylethylamine (161 mL, 0.926 mol), and toluene (200 mL) were combined under argon and heated to reflux for 4 h. The contents of the reaction flask were evaporated in vacuo. Saturated NaHCO₃ was
- 15 added, and the aqueous layer was extracted with ether. The combined

- 90 -

ether extracts were washed with brine, then dried with Na_2SO_4 .
Vacuum distillation afforded the product.

Step 2

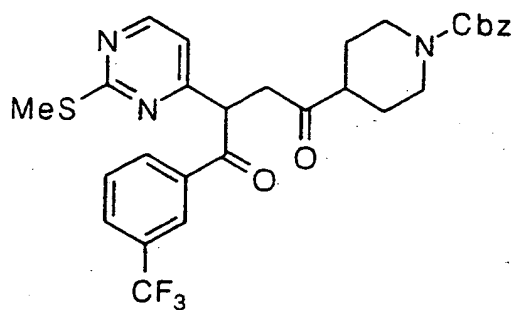


5

The target compound was prepared using the procedure set forth in Example 2, Step 1, replacing 4-picoline with the product of Step 1 and 4-fluoro-[N-methyl-N-methoxy]benzamide with 3-trifluoromethyl-(N-methyl-N-methoxy)benzamide.

10

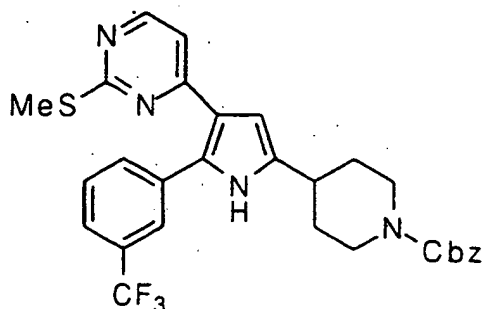
Step 3



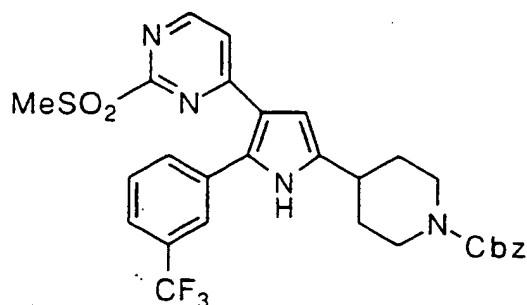
The target compound was prepared using the procedure set forth in Example 2, Step 3, using the product of Step 2.

15

- 91 -

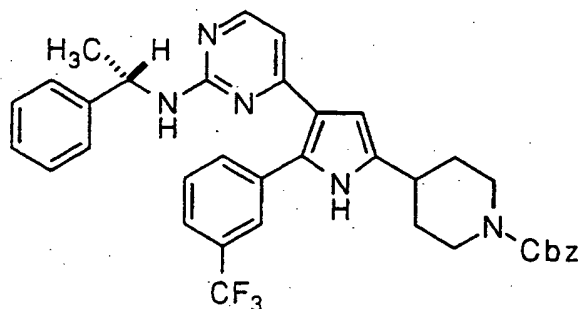
Step 4

The target compound was prepared using the procedure of Example 2, Step 4 and the product of Step 3.

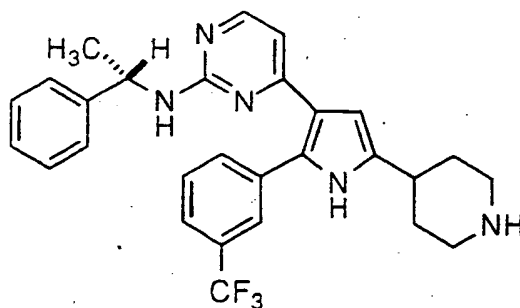
Step 5

10 The product of step 4 (10.34g, 18.7 mmol), sodium tungstate (618 mg, 1.87 mmol), methanol (20 mL), ethyl acetate (100 mL), and 30% hydrogen peroxide (8.50 mL, 74.8 mmol) were combined under argon and heated to reflux. Saturated NaHCO_3 was added and the mixture was extracted with ethyl acetate. The combined
15 organic extracts were washed with brine, then dried with Na_2SO_4 . The mixture was evaporated in vacuo. The residue was flash chromatographed using ethyl acetate:hexane (60:40) to give the product.

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Step 6

The product of Step 5 (998 mg, 1.71 mmol) and s-(-)-alpha-methylbenzylamine (2.20 mmol, 17.1 mmol) were combined and heated to 125°C for 24 hrs. The reaction was poured into sat. NaHCO₃. The aqueous fraction was extracted with methylene chloride, washed with brine, dried with Na₂SO₄ then flash chromatographed using ethyl acetate:hexane (60:40) to yield product.

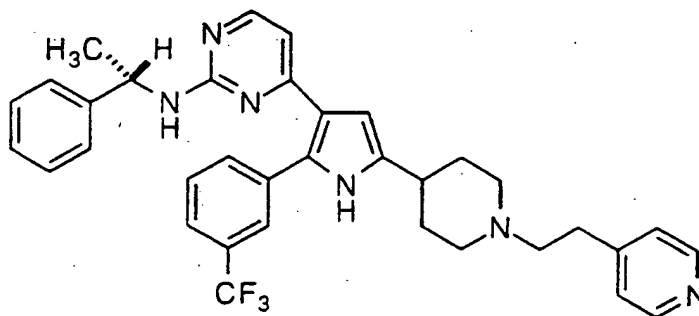
10 Step 7

The product of step 6 (818 mg, 1.34 mmol) and 3N hydrochloric acid (10 mL) were combined and heated to reflux for 24 hrs. The solution was cooled, and washed with ether. The aqueous layer was made basic with NaOH (aq) then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with Na₂SO₄ then flash chromatographed using methylene chloride:methanol:ammonium hydroxide (80:20:2) to produce the target compound as a solid.

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M. P. 123 - 127°C

¹H NMR (300 MHz, CD₃OD) δ: 7.95 (d, 1H); 7.75 - 7.50 (m, 4H);
7.30 - 7.10 (m, 5H); 6.52 (d, 1H); 6.34 (s, 1H); 4.80 (s, br, 1H); 3.40 -
3.20 (m, 3H); 3.00 - 2.80 (m, 3H); 2.15 (d, br, 2H); 1.90 - 1.70 (m,
5 2H); 1.38 (d, 3H).

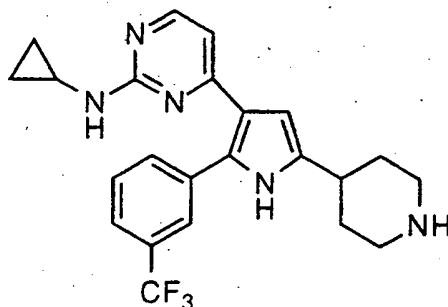
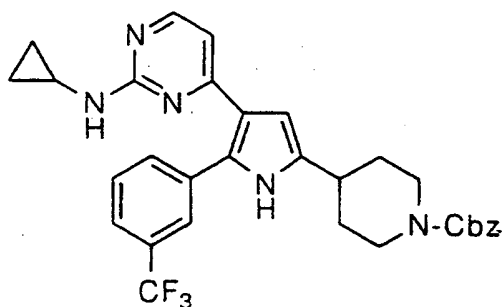
EXAMPLE 117

10 The compound of Example 116 (322 mg, 0.660 mmol),
NaHCO₃ (61 mg, 0.727 mmol), 4-vinylpyridine (0.5 mL, 4.64 mmol),
and methanol (4 mL) were heated at reflux. The reaction mixture was
poured into sat NaHCO₃. The aqueous layer was extracted with
methylene chloride, washed with brine, then dried with Na₂SO₄. Flash
15 column chromatography using methylene chloride:methanol:ammonium
hydroxide (95:5:0.5) yielded the product. Triturated with ether to get a
solid.

M.P. 99 - 109°C.

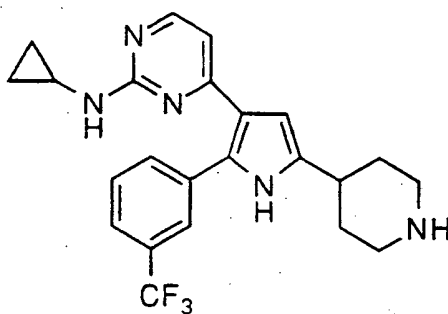
¹H NMR (300 MHz, CDCl₃): 8.50 (d, 2H); 8.40 (s, br, 1H); 8.06 (d,
1H); 7.75 (s, 1H); 7.65 - 7.55 (m, 2H); 7.49 - 7.39 (t, 1H); 7.35 - 7.14
20 (m, 7H); 6.48 (d, 1H); 6.39 (d, 1H); 5.25 (d, 1H); 5.00 (s, br, 1H); 3.10
(d, 2H); 2.90-2.80 (m, 2H); 2.70 - 2.58 (m, 3H); 2.22 - 2.10 (m, 2H);
2.08 - 1.75 (m, 5H); 1.45 (d, 3H).

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EXAMPLE 118Step 1

5

The target compound was prepared using steps 1 - 5 in Example 116, followed by reaction with cyclopropylamine using the procedure of Example 116, Step 6.

10 Step 2

The product of Step 1 (500 mg, 0.886 mmol), methylene chloride (15 mL), and 30% hydrogen bromide in acetic acid (1.82 mL).

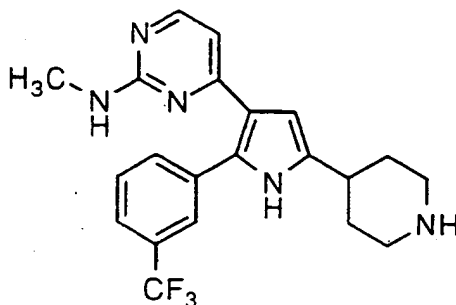
- 95 -

8.86 mmol) were combined with ice cooling under argon. After 2 hrs, the reaction solution was washed with ether. The aqueous layer was made basic with 2N sodium hydroxide, then extracted with ethyl acetate. The product was dried with Na₂SO₄ and crystallized using hexane:ethyl acetate (80:20).

M.P. 208 - 209 °C

¹H NMR (300 MHz, CDCl₃): 8.30 (s, 1H); 8.10 (d, 2H); 7.90 (m, 1H); 7.70 (m, 1H); 7.60 (m, 1H); 7.50 (m, 1H); 6.59 (d, 1H); 6.44 (s, 1H); 5.20 (s, 1H); 3.20 (m, 2H); 2.80 - 2.60 (m, 4H); 2.05 - 1.95 (m, 2H); 1.80 - 1.60 (m, 4H); 0.80 - 0.60 (m, 2H); 0.50 - 0.40 (m, 2H).

EXAMPLE 119

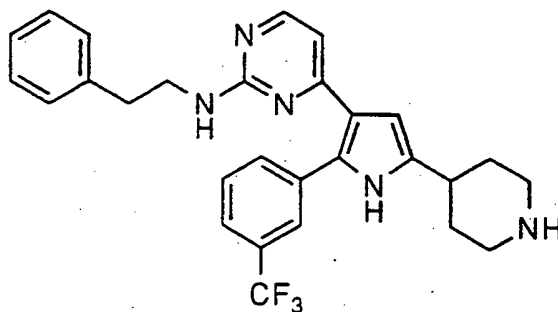


The target compound is prepared the procedure of Example 116, substituting methylamine in step 6.

M.P. 139 - 141 °C

¹H NMR (300 MHz, CDCl₃): 8.35 (s, 1H); 8.10 (d, 1H); 7.80 (s, 1H); 7.70 - 7.40 (m, 3H); 6.50 (m, 2H); 4.90 (s, 1H); 3.25 (d, 2H); 2.90 - 2.70 (m, 6H); 2.10 - 1.90 (m, 3H); 1.80 - 1.60 (m, 2H).

- 96 -

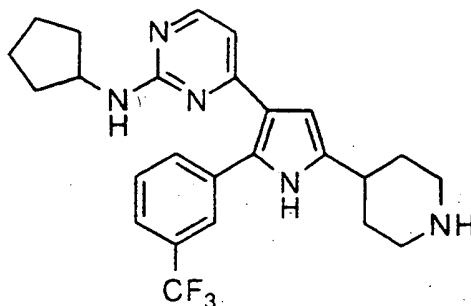
EXAMPLE 120

The target compound is prepared using the procedure of Example 116, substituting phenethylamine in Step 6.

5 M. P. 177 - 178°C

¹H NMR (300 MHz, CDCl₃): 8.30 (s, 1H); 8.10 (d, 1H); 7.75 (s, 1H); 7.65 (d, 1H); 7.50 (d, 1H); 7.45 (t, 1H); 7.33 - 7.10 (m, 4H); 6.50 (d, 1H); 6.45 (d, 1H); 4.95 (m, 1H); 3.60 - 3.40 (m, 2H); 3.20 (m, 2H); 2.85 - 2.66 (m, 5H); 2.00 (m, 2H); 1.80 - 1.60 (m, 2H).

10

EXAMPLE 121

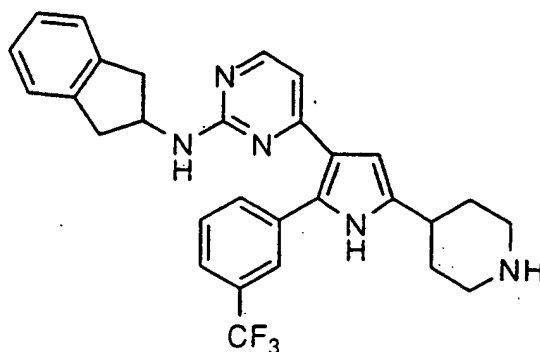
15 The target compound was prepared using the procedure of Example 116, substituting cyclopentylamine in Step 6.

M.P. 231 - 232°C

CHN anal for C₂₅H₂₈F₃N₅ · 0.15 H₂O: Calc C 65.52, H 6.23, N 15.28.

Found: C 65.60, H 6.39, N 14.89.

20

EXAMPLE 122

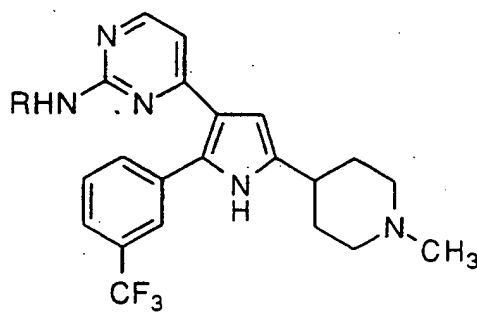
- 5 The target compound was prepared using the procedure of Example 116, substituting 2-aminoindane in Step 6.

M. P. 193 - 194°C

CHN anal for $C_{29}H_{28}F_3N_5 \cdot 0.20 H_2O$: Calc C 68.67, H 5.64, N 13.81.

Found: C 68.63, H 5.65, N 13.67.

- 10 The following compounds were prepared using the procedure set forth in Example 3.



EXAMPLE	R	M.P. (°C)
123	cyclopropyl	180 - 200
124	methyl	121 - 123
125	phenethyl	115 - 117
126*	s- α -Me-benzyl	195 - 205

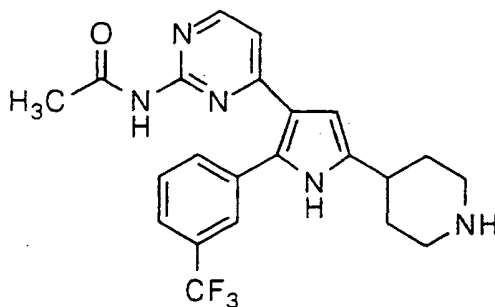
*Characterization data for Example 126 (dihydrochloride salt):

- 98 -

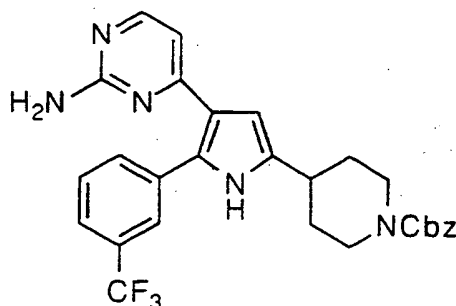
¹H NMR (300 MHz, CD₃OD): 11.70 (s, br, 1H); 7.96 (d, 1H); 7.85 - 7.62 (m, 4H); 7.30 - 7.18 (m, 3H); 7.10 - 6.90 (s, br, 3H); 6.68 (s, 1H); 4.60 (s, br, 1H); 3.65 (d, 2H); 3.30 (m, 3H); 3.25 - 3.10 (t, 2H); 3.00 (m, 1H); 2.30 (d, 2H); 2.00 (m, 2H); 1.40 (m, 2H). CHN anal.

5 Calculated for C₂₉H₃₀F₃N₅ · 2HCl · 1.0 H₂O: C, 58.39; H, 5.75; N, 11.74. Found: C, 58.56; H, 5.90; N, 11.35.

EXAMPLE 127

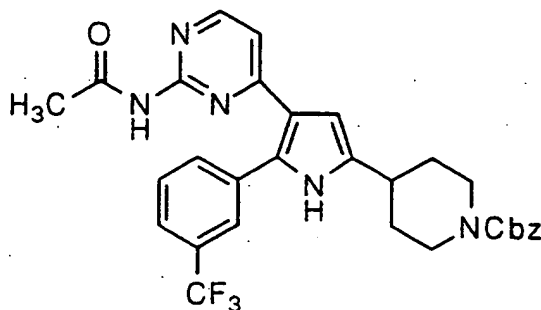


Step 1

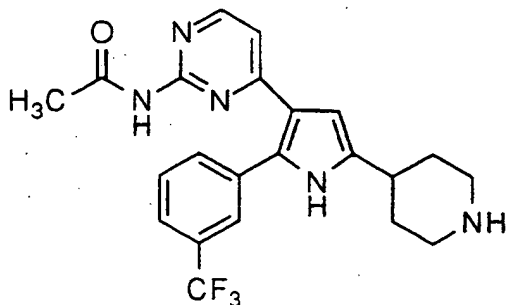


The target compound was prepared using the procedure set forth in Example 116, Steps 1-5, followed by reaction with ammonia in accordance with Example 116, Step 6.

- 99 -

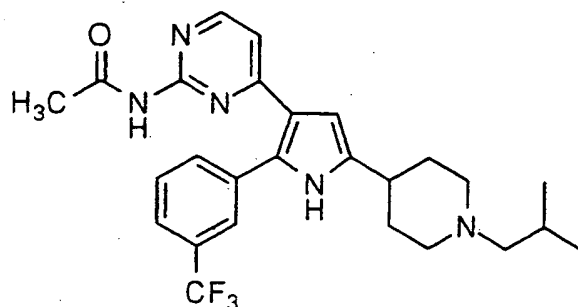
Step 2

The product of step 1 (1.37 g, 2.62 mmol) and methylene chloride (10 mL) were cooled in an ice bath under argon. Acetic anhydride (0.344 mL, 3.65 mmol) and diisopropylethylamine (1.26 mL, 7.30 mmol) were added. The reaction was warmed to room temperature and then heated to reflux. The reaction was poured into sat'd. NaHCO₃. The aqueous fraction was extracted with methylene chloride, dried with Na₂SO₄ then flash chromatographed using ethyl acetate hexane (70:30) to yield a yellow foam.

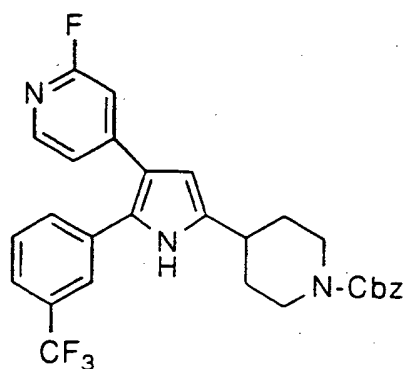
Step 3

The target compound was prepared using the procedure of Example 118, Step 2.
M.P. 130 - 140 °C

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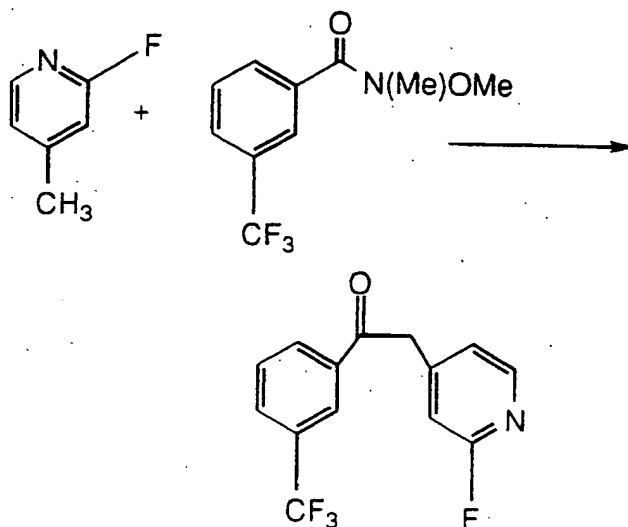
EXAMPLE 128

- 5 The compound of Example 127 (150 mg, 0.350 mmol), 1-bromo-2-methylpropane (0.053 mL, 0.490 mmol), NaHCO₃ (82 mg, 0.980 mmol) and acetonitrile (4 mL) were combined under argon and heated to 90°C. The mixture was poured into sat'd. NaHCO₃ and extracted with methylene chloride. The combined organic extracts were dried with Na₂SO₄ then flash chromatographed using methylene
- 10 chloride:methanol:ammonium hydroxide (98:2:0.2). The target compound was crystallized from ethyl acetate. M. P. 170 - 180°C.

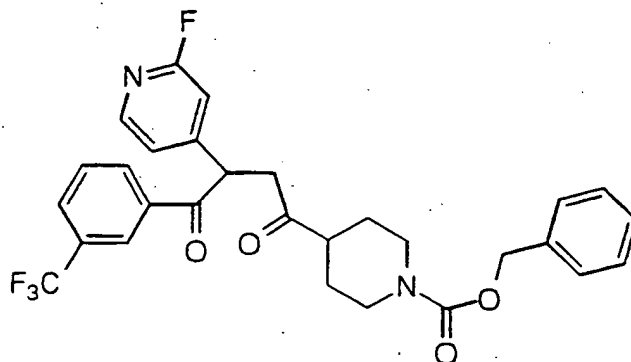
EXAMPLE 129

15

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Step 1

- The procedure described in Example 2, Step 1, but instead using 2-fluoro-4-picoline and 3-trifluoromethyl-(N-methyl-N-methoxy)-benzamide, was followed to give the desired product.
- ^1H NMR (CDCl_3 300 MHz): 4.38 (s, 2H), 6.83 (s, 1H), 7.05 (d, 1H), 7.68 (dd, 1H), 7.89 (d, 1H), 8.20 (dd, 2H), 8.25 (s, 1H).

10 Step 2

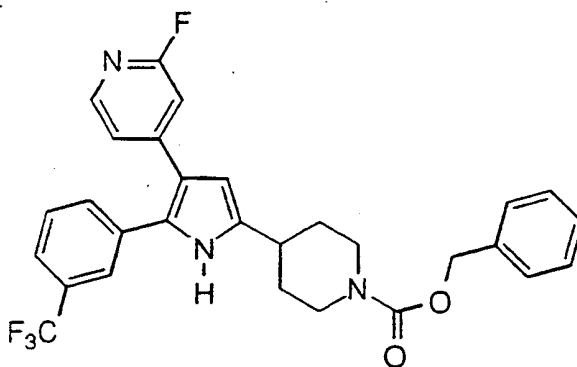
The procedure described in Example 2, step 3, but using sodium hydride (60% dispersion in mineral oil) in place of a 1M

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solution of sodium hexamethyldisilazide in THF, was followed to give the desired product.

¹H-NMR (CDCl₃, 300 MHz): 1.56 (bm, 2H); 1.85 (bm, 2H); 2.58 (m, 1H); 2.81 (dd, 1H); 2.89 (m, 2H); 3.66 (dd, 1H); 4.18 (bm, 2H); 5.14 (m, 3H); 6.84 (s, 1H); 7.10 (d, 1H); 7.35 (m, 5H); 7.58 (dd, 1H); 7.81 (d, 1H); 8.09 (d, 1H); 8.18 (dd, 2H).

Step 3



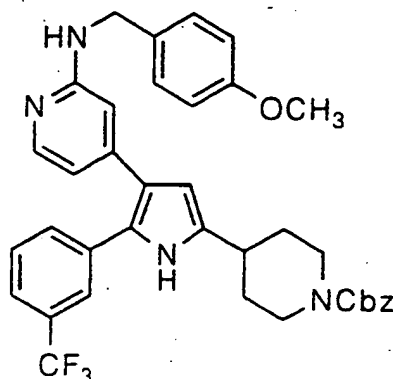
10 The procedure described in Example 2, Step 4 was followed, giving the desired product.

M. P. 184-185° (ethyl acetate-hexanes).

Anal. Calcd. for C₂₉H₂₅F₄N₃O₂: C, 66.53; H, 4.81; N, 8.03. Found: C, 66.49; H, 4.85; N, 7.87.

15

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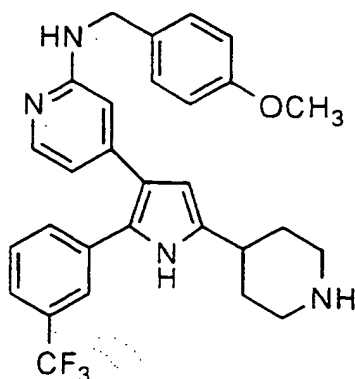
EXAMPLE 130

5 The compound of Example 129 (1.00 g, 1.91 mmol), and p-methoxybenzylamine (3.0 mL, 23.0 mmol) were combined under argon and heated to 130°C for five days. The mixture was poured into sat'd. NaHCO₃ and extracted with methylene chloride. The combined organic extracts were dried with Na₂SO₄. Flash chromatography using hexane:ethyl acetate (60:40) yielded an oil, which was crystallized using
10 methanol.

M.P. 179 - 180°C.

CHN anal. Calculated: C, 69.36; H, 5.51; N, 8.74. Found: C, 69.45; H, 5.58; N, 8.83.

15

EXAMPLE 131

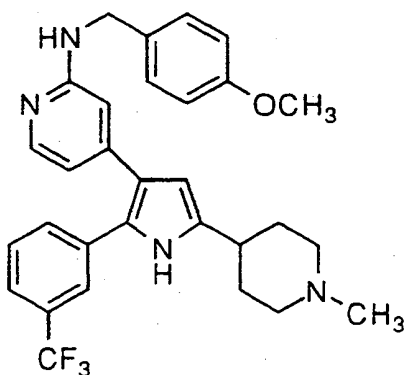
- 104 -

The compound of Example 130 (200 mg, 0.313 mmol) and palladium hydroxide (220 mg) were combined and hydrogenated at 55 psi. After 24 hrs the mixture was filtered and the filtrate evaporated in vacuo. Flash column chromatography using methylene chloride:methanol:ammonium hydroxide (95:5:0.5) yielded the target compound as a white solid.

M.P. 159 - 160°C.

CHN anal. Calculated for $C_{29}H_{29}F_3N_4O \cdot 0.20 H_2O$: C, 68.27; H, 5.81; N, 10.98. Found: C, 68.21; H, 5.63; N, 11.05.

EXAMPLE 132

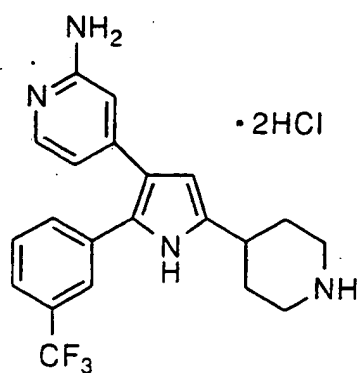
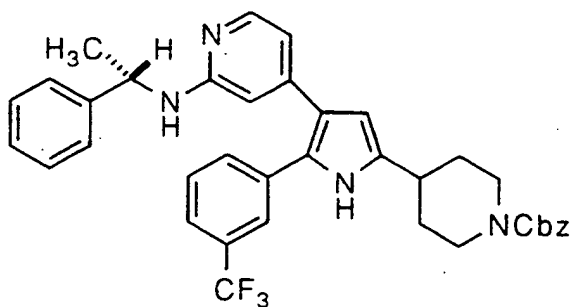


The target compound was prepared using the procedure of Example 3, substituting the compound from Example 130.

M.P. 205 - 206°C.

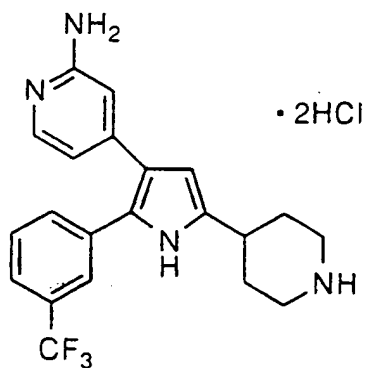
CHN anal. Calculated for $C_{30}H_{31}F_3N_4O \cdot 0.35 H_2O$: C, 68.38; H, 6.06; N, 10.63. Found: C, 68.44; H, 6.02; N, 10.49.

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EXAMPLE 133Step 1

5

The target compound was prepared using the procedure of Example 130, substituting *s*-(-)- α -benzylmethylamine.

10 Step 2

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The target compound as the free base was prepared using the procedure of Example 132, Step 7. The dihydrochloride salt was prepared using 6N hydrogen chloride in ethanol.

M.P. 119 - 135°C.

- 5 CHN anal. Calculated for $C_{21}H_{21}F_3N_4 \cdot 0.45 H_2O$: C, 53.95; H, 5.15; N, 11.99. Found: C, 54.01; H, 5.41; N, 11.99.

BIOLOGICAL ASSAYS.

- 10 The ability of compounds of the present invention to inhibit cytokines can be demonstrated by the following *in vitro* assays.

Lipopolysaccharide mediated production of cytokines

- Human peripheral blood mononuclear cells (PBMC) are isolated from fresh human blood according to the procedure of Chin and
15 Kostura, *J. Immunol.* **151**, 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte
20 separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2×10^6 cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO.

- Lipopolysaccharide (Salmonella type Re545; Sigma Chemicals) is added
25 to the cells to a final concentration of 100 ng/mL. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the test compound, at the appropriate dilution, and incubated for 24 hours. at 37°C in 5% CO₂. At the end of the culture period, cell culture supernatants are assayed for IL-1 β , TNF- α .
30 IL-6 and PGE₂ production using specific ELISA.

IL-1 mediated cytokine production

- Human peripheral blood mononuclear cells are isolated from fresh human blood according to the procedure of Chin and Kostura, *J.*
35 *Immunol.* **151**, 5574-5585 (1993). Whole blood is collected by sterile

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venipuncture into 60 mL syringes coated with 1.0 mL of sodium-heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2×10^6 cell/mL in RPMI cell culture medium containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO. Endotoxin free recombinant human IL- 1β is then added to a final concentration of 50 pMolar. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the compound at the appropriate dilution, and are incubated for 24 hours at 37°C in 5% CO₂. At the end of the culture period, cell culture supernatants are assayed for TNF- α , IL-6 and PGE₂ synthesis using specific ELISA.

15

Determination of IL- 1β , TNF- α , IL-6 and prostanoid production from LPS or IL-1 stimulated PBMC's

IL- 1β ELISA

Human IL- 1β can be detected in cell-culture supernatants or whole blood with the following specific trapping ELISA. Ninety-six well plastic plates (Immulon 4; Dynatech) are coated for 12 hours at 4°C with 1 mg/mL protein-A affinity chromatography purified mouse anti-human IL- 1β monoclonal antibody (purchased as an ascites preparation from LAO Enterprise, Gaithersburg Maryland) diluted in Dulbecco's phosphate-buffered saline (-MgCl₂, -CaCl₂). The plates are washed with phosphate buffered saline (PBS)-Tween (Kirkegaard and Perry) then blocked with 1% BSA diluent and blocking solution (Kirkegaard and Perry) for 60 minutes at room temperature followed by washing with PBS Tween.

30

IL- 1β standards are prepared from purified recombinant IL- 1β produced from *E. coli*. The highest concentration begins at 10 ng/mL followed by 11 two-fold serial dilutions. For detection of IL- 1β from cell culture supernatants or blood plasma, 10 - 25 mL of

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- supernatant is added to each test well with 75 - 90 mL of PBS Tween. Samples are incubated at room temperature for 2 hours then washed 6 times with PBS Tween on an automated plate washer (Dennly). Rabbit anti-human IL-1 β polyclonal antisera diluted 1:500 in PBS-Tween is
- 5 added to the plate and incubated for 1 hour at room temperature followed by six washes with PBS-Tween. Detection of bound rabbit anti-IL-1 β IgG is accomplished with Fab' fragments of Goat anti-rabbit IgG-horseradish peroxidase conjugate (Accurate Scientific) diluted 1:10,000 in PBS-Tween. Peroxidase activity was determined using
- 10 TMB peroxidase substrate kit (Kirkegaard and Perry) with quantitation of color intensity on a 96-well plate Molecular Devices spectrophotometer set to determine absorbance at 450 nM. Samples are evaluated using a standard curve of absorbance versus concentration. Four-parameter logistics analysis generally is used to fit data and obtain
- 15 concentrations of unknown compounds.

TNF- α ELISA

- Immulon 4 (Dynatech) 96-well plastic plates are coated with a 0.5 mg/mL solution of mouse anti-human TNF- α monoclonal antibody.
- 20 The secondary antibody is a 1:2500 dilution of a rabbit anti-human TNF- α polyclonal serum purchased from Genzyme. All other operations are identical to those described above for IL-1 β . The standards are prepared in PBS-Tween + 10% FBS or HS (human serum). Eleven 2 fold dilutions are made beginning at 20 ng/mL TNF-
- 25 α .

IL-6 ELISA

- Levels of secreted human IL-6 are also determined by specific trapping ELISA as described previously in Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). (Dynatech) ELISA plates are
- 30 coated with mouse anti-human IL-6 monoclonal antibody diluted to 0.5 mg/ml in PBS. The secondary antibody, a rabbit anti-human IL-6 polyclonal antiserum, is diluted 1:5000 with PBS-Tween. All other operations are identical to those described above for IL-1 β . The

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standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilutions are made beginning at 50 ng/mL IL-6.

PGE₂ production

5 Prostaglandin E₂ is detected in cell culture supernatants from LPS or IL-1 stimulated PBMC's using a commercially available enzyme immunoassay. The assay purchased from the Cayman Chemical (Catalogue number 514010) and is run exactly according to the manufacturers instructions.

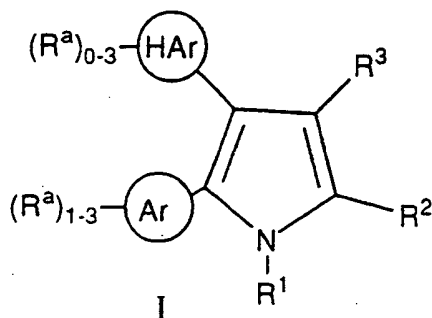
10

Interleukin8 (IL-8)

The present compounds can also be assayed for IL-8 inhibitory activity as discussed below. Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained
15 in culture medium supplemented with 15% fetal bovine serum (FBS) and 1% CS-HBGF (hemoglobin growth factor) consisting of aFGF (acid fibroblast growth factor) and heparin. The cells are then diluted 20-fold before being plated (250 µl) into gelatin coated 96-well plates. Prior to use, culture medium is replaced with fresh medium (200µl). Buffer or
20 test compound (25µl, at appropriate concentrations) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO₂. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems
25 (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC₅₀ values where appropriate are generated by non-linear regression analysis.

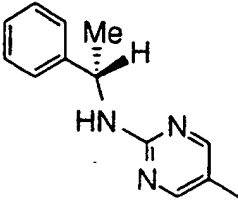
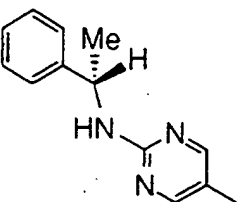
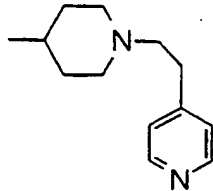
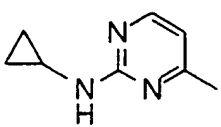
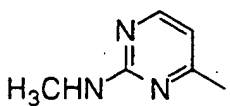
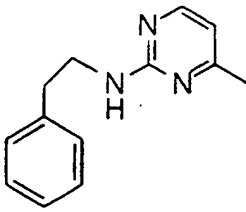
30 The following non-limiting compounds are found to inhibit one or more cytokines at IC₅₀ concentrations of less than 100 µM.

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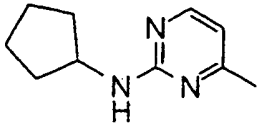
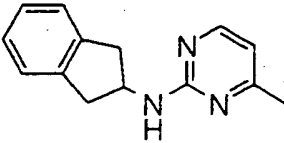
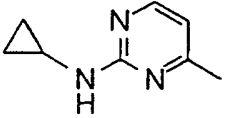
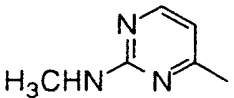
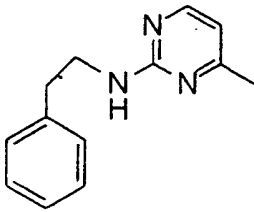
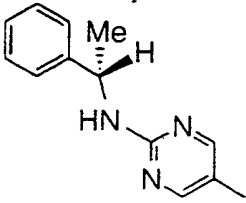


R ¹	(R ^a) ₁₋₃ -Ar	(R ^a) ₀₋₃ -HAr	R ³	R ²
H	4-F-Ph	4-pyridyl	H	t-Bu
H	4-F-Ph	4-pyridyl	H	4-(N-Cbz)-piperidiny
H	4-F-Ph	4-pyridyl	H	4-(N-Me)-piperidiny
H	4-F-Ph	4-quinolinyl	H	4-(N-Cbz)-piperidiny
H	4-F-Ph	4-pyridyl	H	4-piperidiny
H	4-F-Ph	4-quinolinyl	H	4-(N-Me)-piperidiny
H	4-F-Ph	4-pyridyl	H	4-(N-COCH ₂ NH ₂)-piperidiny
H	4-F-Ph	4-pyridyl	H	4-(N-COCH ₃)-piperidiny
H	4-F-Ph	4-pyridyl	H	4-(N-COCH ₂ NH-CO ₂ tBu)piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-CBz)-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	H	4-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-Me)-piperidiny
H	3-(CF ₃)-Ph	4-(2-F)-pyridyl	H	4-(N-CBz)-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-CBz)-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	Me	4-[N-SO ₂ Ph]-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-acetyl)-piperidiny
H	3,4-di-F-Ph	4-pyridyl	Et	4-(N-Me)-piperidiny
H	3,4-di-F-Ph	4-pyridyl	Me	4-(N-Me)-piperidiny
H	3,4-di-F-Ph	4-pyridyl	-CO ₂ Et	4-(N-Me)-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	-CO ₂ Et	4-(N-Me)-piperidiny

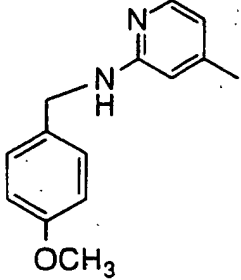
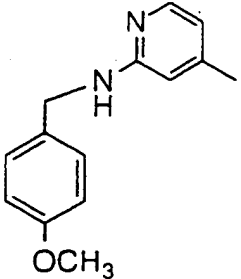
- 111 -

H	3-(CF ₃)-Ph	4-pyridyl	CH ₃	4-(N-Me)-piperidinyI
H	3-(CF ₃)-Ph	4-pyridyl	CH ₃	4-piperidinyI
H	3-(CF ₃)-Ph		H	4-piperidinyI
H	3-(CF ₃)-Ph		H	
H	3-(CF ₃)-Ph		H	4-piperidinyI
H	3-(CF ₃)-Ph		H	4-piperidinyI
H	3-(CF ₃)-Ph		H	4-piperidinyI

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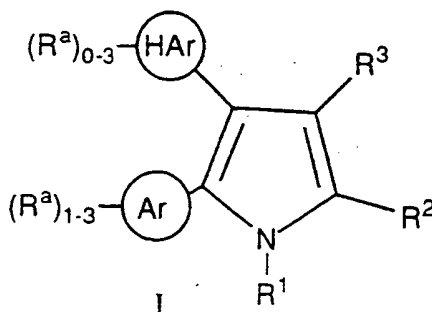
H	3-(CF ₃)-Ph		H	4-piperidinyl
H	3-(CF ₃)-Ph		H	4-piperidinyl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl

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H	3-(CF ₃)-Ph		H	4-piperidiny1
H	3-(CF ₃)-Ph		H	4-(N-Me)-piperidiny1
H	3-(CF ₃)-Ph	4-pyridyl	-CO ₂ Et	4-piperidiny1
H	3-(CF ₃)-Ph	4-pyridyl	-CO ₂ Et	N-(2-ethylpyridin-4-yl)piperidin-4-yl
H	3,4-di-F-phenyl	4-pyridyl	-CO ₂ Et	4-piperidiny1
CH ₃	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-Me)-piperidiny1

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



or a pharmaceutically acceptable salt thereof, wherein:

Ar represents a C₅₋₁₀ aryl or heteroaryl group, said aryl or heteroaryl group being substituted with 1 - 3 groups selected from R^a;

HAr represents a heteroaryl group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 - 3 R^a groups;

each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²⁰; CO₂R²³; CONR²⁰R²³; SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰; C(NR²⁰)NR²⁰R²³; CONR²⁰SO₂R²¹ and SO₂NR²⁰CO₂R²¹;

R¹ is selected from the group consisting of: H; C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, aryl, alkynyl and heterocyclyl being optionally substituted with from

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one to three members selected from the group consisting of: aryl, heteroaryl, OR^{20} , SR^{20} , $N(R^{20})_2$, $S(O)R^{21}$, SO_2R^{21} , $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, and $C(O)OCH_2OC(O)R^{20}$;

R^2 is selected from the group consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, and C_{2-15} alkynyl, heterocyclyl, said alkyl, alkenyl and alkynyl optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, $S(O)$, SO_2 or NR^{24} ; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl(R^a) $_0-3$, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$, $S(O)R^{23}$, SO_2R^{23} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{21}$, $NR^{20}COR^{23}$, $NR^{20}CO_2R^{23}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{23}$ and $OCONR^{20}R^{21}$;

R^3 is selected from the group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, CF_3 , OCF_3 , NO_2 , heterocyclyl, CN, $S(O)R^{21}$, SO_2R^{21} , COR^{20} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and $SO_2NR^{20}CO_2R^{21}$; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, CN, aryl, heteroaryl, OR^{20} , SR^{20} , $NR^{20}R^{23}$, $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{21}$ and $OCONR^{20}R^{23}$;

R^{20} represents a member selected from the group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, aryl, heteroaryl, heterocyclyl

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and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

R^{21} represents a member selected from the group
 5 consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl optionally interrupted by oxo and/or 1-2 heteroatoms selected from O, S, S(O), SO_2 or NR^{24} ; said alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl being optionally substituted with from 1-3 of halo,
 10 heterocyclyl, aryl, heteroaryl, CN, OR^{20} , $O((CH_2)_nO)_mR^{20}$, $NR^{20}((CH_2)_nO)_mR^{20}$ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR^{20} , $NR^{20}R^{23}$, $S(O)R^{22}$, SO_2R^{22} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CONR^{20}R^{23}$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CONR^{20}R^{23}$, $NR^{22}C(NR^{22})NHR^{22}$,
 15 CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, and $OCONR^{20}R^{23}$;

R^{22} is selected from the group consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, said
 20 alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

R^{23} is R^{21} or H;

25 R^{24} is selected from aryl, COR^{22} , CO_2R^{22} , $CON(R^{20})_2$, R^{23} and SO_2R^{22} ;

and when two R^{20} groups are present, when R^{20} and R^{21} are present, or when R^{20} and R^{23} are present, said two R^{20} groups, R^{20}
 30 and R^{21} or said R^{20} and R^{23} may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

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2. A compound in accordance with claim 1 wherein



represents a member selected from the group consisting of:
phenyl, pyridyl, pyrimidinyl, thiophenyl, furanyl, imidazolyl, thiazolyl,
5 isothiazolyl, oxazolyl and isoxazolyl.

3. A compound in accordance with claim 1 wherein R^a
is selected from the group consisting of: halo, CN, R²¹, OR²³,
CO₂R²³ and CONR²⁰R²³.

10

4. A compound in accordance with claim 1 wherein



represents a member selected from the group consisting of:
pyridyl, quinolyl, purinyl, imidazolyl, pyrimidinyl and imidazopyridyl.

15

5. A compound in accordance with claim 1 wherein R¹
is a member selected from the group consisting of: H, C₁-15 alkyl and
substituted C₁-15 alkyl.

20 6. A compound in accordance with claim 1 wherein R²
represents a member selected from one of the following groups:

a) -C₁-7-straight or branched alkyl optionally
interrupted by oxo or NR²⁴ and optionally substituted by 1-3 groups
selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃,
heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³,
25 SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³,
NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³,
CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³
and OCONR²⁰R²¹;

30 b) -C₄-7-cycloalkyl optionally interrupted by oxo or
NR²⁴ and optionally substituted by 1-3 groups selected from the group
consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰,
NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,

SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³,
N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹,
NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

c) -C₁₋₄-alkyl-aminoacyl-C₂₋₆-alkyl, the alkyl portions
5 thereof being optionally interrupted by oxo or NR²⁴, and optionally
substituted by 1-3 groups selected from the group consisting of: halo,
heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³,
SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹,
NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰,
10 CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹,
SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

d) -C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl, the alkyl
portions thereof being optionally interrupted by oxo or NR²⁴, and
optionally substituted by 1-3 groups selected from the group consisting
15 of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³,
S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³,
N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹,
NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

e) -C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl, the alkyl
portions thereof being optionally interrupted by oxo or NR²⁴, and
optionally substituted by 1-3 groups selected from the group consisting
of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³,
S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
25 SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³,
N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹,
NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;
and

f) -C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl, the
30 alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and
optionally substituted by 1-3 groups selected from the group consisting
of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³,
S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³,

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$N(R^{20})C(NR^{20})NHR^{20}$, CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$,
 $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}SO_2R^{23}$ and $OCONR^{20}R^{21}$.

7. A compound in accordance with claim 1 wherein R^3
 5 represents a member selected from the group consisting of:

- a) H,
- b) alkyl,
- c) halo,
- d) CO_2R^{20} ,
- 10 e) $CONR^{20}R^{23}$ and
- f) CN.

8. A compound in accordance with claim 1 wherein:

15 $\textcircled{\text{Ar}}$ is selected from the group consisting of:

- a) phenyl,
- b) pyridyl,
- c) pyrimidinyl,
- d) thiophenyl,
- 20 e) furanyl,
- f) imidazolyl,
- g) thiazolyl,
- h) isothiazolyl,
- i) oxazolyl, and
- 25 j) isoxazolyl;

R^a represents a member selected from the group consisting of: halo,
 CN, R^{21} , OR^{23} , CO_2R^{23} and $CONR^{20}R^{23}$;

30 $\textcircled{\text{HAr}}$ is selected from the group consisting of:

- a) pyridyl,
- b) quinolyl,

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- c) purinyl,
- d) imidazolyl,
- e) pyrimidinyl and
- f) imidazopyridine;

5

R¹ is:

- a) H or
- b) C₁₋₁₅ alkyl unsubstituted or substituted with 1-3

10 groups selected from the group consisting of: aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹ and C(O)OCH₂OC(O)R²⁰;

15

R² is selected from the group consisting of:

a) -C₁₋₇-straight or branched alkyl optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

25

b) -C₄₋₇-cycloalkyl optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

30

c) -C₁₋₄-alkyl-aminoacyl-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo,

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heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹,
 5 SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

d) -C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³,
 10 S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

e) -C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
 15 SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹.
 20 and

f) -C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴, and optionally substituted by 1-3 groups selected from the group consisting of: halo, heterocyclyl, aryl(R^a)₀₋₃, heteroaryl, OR²⁰, SR²⁰, NR²⁰R²³, S(O)R²³, SO₂R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
 25 SO₂NR²⁰CONR²⁰R²¹, NR²⁰COR²³, NR²⁰CO₂R²³, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹,
 30 NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰SO₂R²³ and OCONR²⁰R²¹;

R³ is selected from the group consisting of:

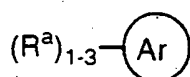
- a) H,
- b) alkyl,

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- c) halo,
- d) CO_2R^{20} ,
- e) $\text{CONR}^{20}\text{R}^{23}$ and
- f) CN.

5

9. A compound in accordance with claim 1 wherein:



is selected from the group consisting of:

10

- a) 4-fluorophenyl,
- b) 4-chlorophenyl,
- c) 3-fluorophenyl,
- d) 3-chlorophenyl,
- e) 4-fluorothiophen-2-yl,
- f) 4-fluorothiophen-3-yl,
- g) 5-fluorothiophen-2-yl,
- h) 5-fluorothiophen-3-yl,
- i) 4-chlorothiophen-2-yl,
- j) 4-chlorothiophen-3-yl,
- k) 5-chlorothiophen-2-yl,
- l) 5-chlorothiophen-3-yl,

15

20

- m) 3-methylphenyl,
- n) 3,4-dichlorophenyl,
- o) 3-hydroxyphenyl,
- p) 2-chlorophenyl,
- q) 4-aminomethylphenyl,
- r) 4-nitrophenyl,
- s) 3,4-difluorophenyl,
- t) 2-methoxyphenyl,

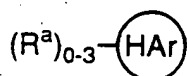
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30

- u) 3-methoxyphenyl,
- v) 4-methoxyphenyl,
- w) 4-(4-(N-acetyl)-piperazinyl)-phenyl,
- x) 4-morpholinyl-phenyl,
- y) 3-trifluoromethylphenyl.

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- z) 4-methylsulfinylphenyl, and
 aa) 4-methylsulfonylphenyl;



is selected from the group consisting of:

- 5 a) 4-pyridyl,
 b) 4-(2-methylpyridyl),
 c) 4-(2-aminopyridyl),
 d) 4-(2-methoxypyridyl),
 e) 4-quinolinyl,
 10 f) 4-pyrimidinyl,
 g) 9-purinyl,
 h) 7-(imidazo[4,5-b]pyridyl),
 i) 4-(3-methylpyridyl),
 j) 2-pyrimidinyl,
 15 k) 3-pyridazinyl,
 l) 2-pyrazinyl,
 m) 2-(N-t-butoxycarbonylamino)-4-pyridyl,
 n) 4-(2-N-acetylamino)-pyridyl,
 o) 4-(2-N-benzoylamino-3-methyl)-pyridyl and
 20 p) 4-(2-N-benzoylamino)-pyridyl;

R¹ is: H;

R² is selected from the group consisting of:

- 25 a) isopropyl,
 b) tert-butyl,
 c) phenethyl,
 d) benzyl,
 e) 2-amino-2,2-dimethylethyl,
 30 f) 4-aminomethylbenzyl,
 g) piperidin-4-yl,
 h) piperidin-3-yl,
 i) pyrrolidin-3-yl,

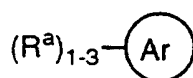
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- 5 j) N-methylpiperidin-4-yl,
 k) N-benzylpiperidin-4-yl,
 l) N-(2-hydroxyethyl)piperidin-4-yl,
 m) N-methanesulfonylpiperidin-4-yl,
 n) isobutyl,
 o) N-(benzyloxycarbonyl)-piperidin-4-yl,
 p) N-morpholinylmethyl
 q) N-(phenyl)-piperidin-4-yl,
 r) N-(methyl)-piperidin-4-yl-methyl,
 10 s) N-methyl-piperidin-3-yl,
 and

R³ is selected from the group consisting of:

- 15 a) H,
 b) F,
 c) Cl,
 d) Br,
 d) CO₂R²⁰,
 e) CONR²⁰R²³ and
 20 f) CN.

10. A compound in accordance with claim 1 wherein:

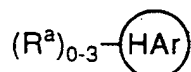


is selected from the group consisting of:

- 25 a) 4-fluorophenyl,
 b) 4-chlorophenyl,
 c) 3-fluorophenyl,
 d) 3-chlorophenyl,
 e) 4-fluorothiophen-2-yl,
 f) 4-fluorothiophen-3-yl,
 30 g) 5-fluorothiophen-2-yl,
 h) 5-fluorothiophen-3-yl,
 i) 4-chlorothiophen-2-yl,
 j) 4-chlorothiophen-3-yl,
 k) 5-chlorothiophen-2-yl.

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- 5 l) 5-chlorothiophen-3-yl,
 m) 3-methylphenyl,
 n) 3,4-dichlorophenyl,
 o) 3-hydroxyphenyl,
 p) 2-chlorophenyl,
 q) 4-aminomethylphenyl,
 r) 4-nitrophenyl,
 s) 3,4-difluorophenyl,
 t) 2-methoxyphenyl,
 10 u) 3-methoxyphenyl,
 v) 4-methoxyphenyl,
 w) 4-(4-(N-acetyl)-piperazinyl-phenyl),
 x) 4-morpholinyl-phenyl,
 y) 3-trifluoromethylphenyl,
 15 z) 4-methylsulfinylphenyl, and
 aa) 4-methylsulfonylphenyl;



is selected from the group consisting of:

- 20 a) 4-pyridyl,
 b) 4-(2-methylpyridyl),
 c) 4-(2-aminopyridyl),
 d) 4-(2-methoxypyridyl),
 e) 4-quinolinyl,
 f) 4-pyrimidinyl,
 25 g) 9-purinyl,
 h) 7-(imidazo[4,5-b]pyridyl),
 i) 4-(3-methylpyridyl),
 j) 2-pyrimidinyl,
 k) 3-pyridazinyl,
 30 l) 2-pyrazinyl,
 m) 2-(N-t-butoxycarbonylamino)-4-pyridyl,
 n) 4-(2-N-acetylamino)-pyridyl,
 o) 4-(2-N-benzolylamino-3-methyl)-pyridyl and

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p) 4-(2-N-benzoylamino)-pyridyl;

 R^1 is: C₁₋₁₅ alkyl;5 R^2 is selected from the group consisting of:

- a) isopropyl,
- b) tert-butyl,
- c) phenethyl,
- d) benzyl,
- 10 e) 2-amino-2,2-dimethylethyl,
- f) 4-aminomethylbenzyl,
- g) piperidin-4-yl,
- h) piperidin-3-yl,
- i) pyrrolidin-3-yl,
- 15 j) N-methylpiperidin-4-yl,
- k) N-benzylpiperidin-4-yl,
- l) N-(2-hydroxyethyl)piperidin-4-yl,
- m) N-methanesulfonylpiperidin-4-yl,
- n) isobutyl.
- 20 o) N-(benzyloxycarbonyl)-piperidin-4-yl,
- p) N-morpholinylmethyl
- q) N-(phenyl)-piperidin-4-yl,
- r) N-(methyl)-piperidin-4-yl-methyl,
- s) N-methyl-piperidin-3-yl,
- 25 and

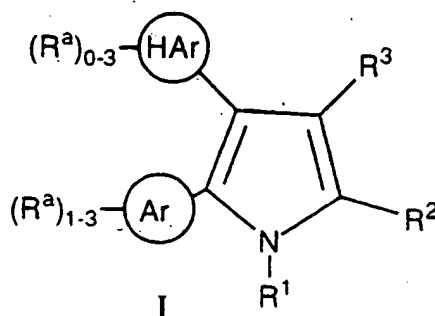
 R^3 is selected from the group consisting of:

- a) H.
- b) F.
- 30 c) Cl,
- d) Br,
- d) CO₂R²⁰,
- e) CONR²⁰R²³ and
- f) CN.

35

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11. A compound represented by formula I:



5 or a pharmaceutically acceptable salt thereof, wherein:



represents a C₅₋₁₀ aryl or heteroaryl group, substituted with 1 - 3 groups selected from R^a;



10 represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 - 3 R^a groups;

15 each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²⁰, CO₂R²³; CONR²⁰R²³; SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; SO₂NR²⁰CO₂R²¹; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰ and C(NR²⁰)NR²⁰R²³;

25 R¹ is selected from the group consisting of: H; C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, aryl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂N(R²⁰)₂,

SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²¹, NR²⁰CO₂R²¹,
 NR²⁰CON(R²⁰)₂, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CON(R²⁰)₂,
 CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCON(R²⁰)₂,
 OCONR²⁰SO₂R²¹, C(O)OCH₂OC(O)R²⁰ and OCONR²⁰R²³;

5

R² is selected from the group consisting of: C₁₋₁₅ alkyl,
 C₂₋₁₅ alkenyl, and C₂₋₁₅ alkynyl, heterocyclyl, optionally interrupted by
 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴; said alkyl,
 alkenyl, alkynyl and heterocyclyl being optionally substituted with from
 10 1-3 of halo, aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²²,
 SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²²,
 NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, N(R²²)C(NR²²)NHR²², CO₂R²⁰,
 CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²²,
 OCONR²⁰SO₂R²² and OCONR²⁰R²³;

15

R³ is selected from the group consisting of: H, C₁₋₁₅ alkyl,
 C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, CF₃, NO₂ and heterocyclyl, said
 alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with
 from one to three members selected from the group consisting of: halo,
 20 CN, aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²²,
 SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²²,
 NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰,
 CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²²,
 OCONR²⁰SO₂R²² and OCONR²⁰R²³;

25

R²⁰ represents a member selected from the group
 consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl,
 aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally
 substituted with 1-3 groups selected from halo, aryl and heteroaryl;

30

R²¹ represents a member selected from the group
 consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, aryl and
 heteroaryl, optionally interrupted by 1-2 heteroatoms selected from O,
 S, S(O), SO₂ or NR²⁴; said alkyl, alkenyl, alkynyl, aryl and heteroaryl

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being optionally substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂,
 5 SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;

10 R²² is selected from the group consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

15 R²³ is R²¹ or H;

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂, R²³ and SO₂R²²;

20 n is 1-4;

m is 1-4;

and when two R²⁰ groups are present, when R²⁰ and R²¹
 25 are present, or when R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally
 30 containing 1-3 additional N atoms and 0-1 additional O or S atom.

12. A compound in accordance with claim 11 wherein:



is selected from the group consisting of:

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- 5
- a) phenyl,
 - b) pyridyl,
 - c) pyrimidinyl,
 - d) thiophenyl,
 - e) furanyl,
 - f) imidazolyl,
 - g) thiazolyl,
 - h) isothiazolyl,
 - i) oxazolyl and
 - 10 j) isoxazolyl;

- (HAr)
- is selected from the group consisting of:
- 15
- a) pyridyl,
 - b) quinolyl,
 - c) purinyl,
 - d) imidazolyl and
 - e) imidazopyridyl;

- R¹ is:
- 20
- a) H or
 - b) substituted alkyl;

- R² is selected from the group consisting of:
- 25
- a) -C₁₋₇-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo or NR²³,
 - b) -C₄₋₇-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo or NR²³,
 - c) -C₁₋₄-alkyl-aminoacyl-C₂₋₆-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo or NR²³,
 - 30 d) -C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³ or NR²⁴.
 - e) -C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³ or

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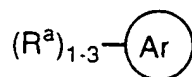
f) -C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³ or NR²⁴; wherein the point of attachment to the pyrrole is from the left hand side of the items listed in a through f; and

5

R³ is: a) H,
b) alkyl,
c) halo, or
d) CO₂R²⁰.

10

13. A compound in accordance with claim 11 wherein:



is selected from the group consisting of:

15

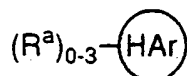
- a) phenyl,
- b) 4-fluorophenyl,
- c) 4-chlorophenyl,
- d) 3-fluorophenyl,
- e) 3-chlorophenyl,
- f) thiophen-2-yl,
- g) thiophen-3-yl,
- h) 4-fluorothiophen-2-yl,
- i) 4-fluorothiophen-3-yl,
- j) 5-fluorothiophen-2-yl,
- k) 5-fluorothiophen-3-yl,
- l) 4-chlorothiophen-2-yl,
- m) 4-chlorothiophen-3-yl,
- n) 5-chlorothiophen-2-yl,
- o) 5-chlorothiophen-3-yl,
- p) 3-methylphenyl,
- q) 3,4-dichlorophenyl, and
- r) 3-hydroxyphenyl;

20

25

30

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is selected from the group consisting of:

- 5
- a) 4-pyridyl,
 - b) 4-(2-methylpyridyl),
 - c) 4-(2-aminopyridyl),
 - d) 4-(2-methoxypyridyl),
 - e) 4-quinolyl,
 - f) 4-pyrimidinyl,
 - g) 9-purinyl,
 - h) 7-(imidazo[4,5-b]pyridinyl), and
 - 10 i) 4-(3-methylpyridyl);

R¹ is: H;R² is selected from the group consisting of:

- 15
- a) isopropyl,
 - b) tert-butyl,
 - c) phenethyl,
 - d) benzyl,
 - e) 2-amino-2,2-dimethylethyl,
 - 20 f) 4-aminomethylbenzyl,
 - g) glycylaminomethyl,
 - h) (L)-alanylaminomethyl,
 - i) 2-amino-2,2-dimethylacetylaminomethyl,
 - j) N,N-dimethylaminoethyl-N-
 - 25 methylaminocarbonylaminomethyl,
 - k) 3-piperidinecarbonylaminomethyl,
 - l) 4-piperidinecarbonylaminomethyl,
 - m) piperidin-4-yl,
 - n) piperidin-3-yl,
 - 30 o) pyrrolidin-3-yl,
 - p) N-methylpiperidin-4-yl,
 - q) N-benzylpiperidin-4-yl,
 - r) N-(2-hydroxyethyl) piperidin-4-yl and

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s) N-methanesulfonylpiperidin-4-yl; and

R³ is selected from the group consisting of:

- 5
- a) H,
 - b) F,
 - c) Cl and
 - d) Br.

14. A compound in accordance with claim 11 wherein:

10 Ar is phenyl.

15. A compound in accordance with claim 11 wherein:

15 HAr is selected from the group consisting of:

- a) pyridyl,
- b) quinolyl,
- c) purinyl,
- d) imidazolyl,
- e) imidazopyridine or
- f) pyrimidinyl.

20

16. A compound in accordance with claim 11 wherein R¹ is:

- 25
- a) H or
 - b) substituted or unsubstituted C₁₋₁₅ alkyl.

25

17. A compound in accordance with claim 11 wherein:
R² is:

- 30
- a) C₁₋₇-straight or branched alkyl optionally interrupted by oxo or NR²⁴ and optionally substituted by : NR²⁰R²³;
 - b) C₄₋₇-cycloalkyl optionally interrupted by oxo or NR²⁴ and optionally substituted by : NR²⁰R²³;

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c) C₁₋₄-alkyl-aminoacyl-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴ and optionally substituted by : NR^{20R23};

5 d) C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴ and optionally substituted by : NR^{20R23};

e) C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴ and optionally substituted by : NR^{20R23}; or

10 f) C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR²⁴ and optionally substituted by: NR^{20R23}; wherein the point of attachment to the pyrrole is from the left hand side of the items listed in a through f.

15 18. A compound in accordance with claim 11 wherein R^a is selected from the group consisting of: halo; CN, R²¹, OR²³, CO₂R²³, CONR^{20R23} and tetrazol-5-yl.

20 19. A compound in accordance with claim 11 wherein R³ is selected from the group consisting of:

- 25 a) H,
b) halo,
c) alkyl,
d) CO₂R²⁰,
e) CONR^{20R23} or
f) CN.

20. A compound in accordance with claim 11 wherein:

30 Ar is selected from the group consisting of:
a) phenyl,
b) pyridyl,
c) pyrimidinyl,
d) thiophenyl,
e) furanyl.

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- f) imidazolyl,
- g) thiazolyl,
- h) isothiazolyl,
- i) oxazolyl, and
- 5 j) isoxazolyl;

R^a is selected from the group consisting of: halo; CN, R^{21} , OR^{23} , CO_2R^{23} , $CONR^{20}R^{23}$ and tetrazol-5-yl.

- (HAr)
- is selected from the group consisting of:
- 10 a) pyridyl,
 - b) quinolyl,
 - c) purinyl,
 - d) imidazolyl,
 - e) pyrimidinyl and
 - 15 f) imidazopyridine;

R^1 is: H or unsubstituted or substituted alkyl;

- R^2 is selected from the group consisting of:
- 20 a) C_{1-7} -straight or branched alkyl optionally interrupted by oxo or NR^{24} and optionally substituted by : $NR^{20}R^{23}$;
 - b) C_{4-7} -cycloalkyl optionally interrupted by oxo or NR^{24} and optionally substituted by : $NR^{20}R^{23}$;
 - c) C_{1-4} -alkyl-aminoacyl- C_{2-6} -alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} and optionally substituted by : $NR^{20}R^{23}$;
 - d) C_{1-4} -alkyl-aminoacyl- C_{4-7} -cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} and optionally substituted by : $NR^{20}R^{23}$;
 - 30 e) C_{1-4} -alkyl-aminoacylamino- C_{2-6} -alkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} and optionally substituted by : $NR^{20}R^{23}$; or
 - f) C_{1-4} -alkyl-aminoacylamino- C_{4-7} -cycloalkyl, the alkyl portions thereof being optionally interrupted by oxo or NR^{24} and

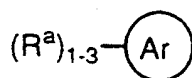
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optionally substituted by: $\text{NR}^{20}\text{R}^{23}$; wherein the point of attachment to the pyrrole is from the left hand side of the items listed in a through f; and

5 R^3 is selected from the group consisting of:

- a) H,
- b) halo,
- c) alkyl,
- d) CO_2R^{20} ,
- 10 e) $\text{CONR}^{20}\text{R}^{23}$ or
- f) CN.

21. A compound in accordance with claim 11 wherein:

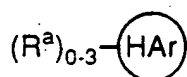


is selected from the group consisting of:

- 15 a) 4-fluorophenyl,
- b) 4-chlorophenyl,
- c) 3-fluorophenyl,
- d) 3-chlorophenyl,
- e) 4-fluorothiophen-2-yl,
- 20 f) 4-fluorothiophen-3-yl,
- g) 5-fluorothiophen-2-yl,
- h) 5-fluorothiophen-3-yl,
- i) 4-chlorothiophen-2-yl,
- j) 4-chlorothiophen-3-yl,
- 25 k) 5-chlorothiophen-2-yl,
- l) 5-chlorothiophen-3-yl,
- m) 3-methylphenyl,
- n) 3,4-dichlorophenyl,
- o) 3-hydroxyphenyl,
- 30 p) 2-chlorophenyl,
- q) 4-aminomethylphenyl,
- r) 4-nitrophenyl,
- s) 3,4-difluorophenyl,
- t) 2-methoxyphenyl.

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- 5
- u) 3-methoxyphenyl,
 - v) 4-methoxyphenyl,
 - w) 4-(4-(N-COCH₃)-piperazinyl-Ph,
 - x) 4-morpholinyl-Ph,
 - y) 3-trifluoromethylphenyl,
 - z) 4-methylsulfinylphenyl, and
 - aa) 4-methylsulfonylphenyl;



is selected from the group consisting of:

- 10
- a) 4-pyridyl,
 - b) 4-(2-methylpyridyl),
 - c) 4-(2-aminopyridyl),
 - d) 4-(2-methoxypyridyl),
 - e) 4-quinolinyl,
 - 15 f) 4-pyrimidinyl,
 - g) 9-purinyl,
 - h) 7-(imidazo[4,5-b]pyridinyl),
 - i) 4-(3-methylpyridyl),
 - j) 2-pyrimidinyl,
 - 20 k) 3-pyridazinyl,
 - l) 2-pyrazinyl,
 - m) 2-(N-t-butoxycarbonylamino)-4-pyridyl,
 - n) 4-(2-N-acetylamino)-pyridyl,
 - o) 4-(2-N-benzolylamino-3-methyl)-pyridyl and
 - 25 p) 4-(2-N-benzolylamino)-pyridyl;

R¹ is: H;R² is selected from the group consisting of:

- 30
- a) isopropyl,
 - b) tert-butyl,
 - c) phenethyl,
 - d) benzyl.

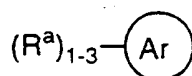
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- 5
- e) 2-amino-2,2-dimethylethyl,
 - f) 4-aminomethylbenzyl,
 - g) piperidin-4-yl,
 - h) piperidin-3-yl,
 - i) pyrrolidin-3-yl,
 - j) N-methylpiperidin-4-yl,
 - k) N-benzylpiperidin-4-yl,
 - l) N-(2-hydroxy-ethyl)piperidin-4-yl,
 - 10 m) N-methanesulfonylpiperidin-4-yl,
 - n) isobutyl,
 - o) N-CBz-piperidin-4-yl,
 - p) N-Bn-piperidin-4-yl,
 - q) N-Ph-piperidin-4-yl,
 - r) CH₂-4-(N-Me)-piperidin-4-yl,
 - 15 s) 3-N-Me-piperidiny, and
 - t) CH₂-morpholin-1-yl,

R³ is selected from the group consisting of:

- 20
- a) H,
 - b) F,
 - c) Cl,
 - d) Br,
 - d) CO₂R²⁰,
 - e) CONR²⁰R²³ or
 - 25 f) CN.

22. A compound in accordance with claim 11 wherein:

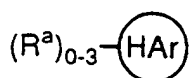


is selected from the group consisting of:

- 30
- a) 4-fluorophenyl,
 - b) 4-chlorophenyl,
 - c) 3-fluorophenyl,
 - d) 3-chlorophenyl,
 - e) 4-fluorothiophen-2-yl.

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- 5
- 10
- 15
- 20
- f) 4-fluorothiophen-3-yl,
 - g) 5-fluorothiophen-2-yl,
 - h) 5-fluorothiophen-3-yl,
 - i) 4-chlorothiophen-2-yl,
 - j) 4-chlorothiophen-3-yl,
 - k) 5-chlorothiophen-2-yl,
 - l) 5-chlorothiophen-3-yl,
 - m) 3-methylphenyl,
 - n) 3,4-dichlorophenyl,
 - o) 3-hydroxyphenyl,
 - p) 2-chlorophenyl,
 - q) 4-aminomethylphenyl,
 - r) 4-nitrophenyl,
 - s) 3,4-difluorophenyl,
 - t) 2-methoxyphenyl,
 - u) 3-methoxyphenyl,
 - v) 4-methoxyphenyl,
 - w) 4-(4-(N-COCH₃)-piperazinyl-Ph,
 - x) 4-morpholinyl-Ph,
 - y) 3-trifluoromethylphenyl,
 - z) 4-methylsulfinylphenyl, and
 - aa) 4-methylsulfonylphenyl;



is selected from the group consisting of:

- 25
- 30
- a) 4-pyridyl,
 - b) 4-(2-methylpyridyl),
 - c) 4-(2-aminopyridyl),
 - d) 4-(2-methoxypyridyl),
 - e) 4-quinolinyl,
 - f) 4-pyrimidinyl,
 - g) 9-purinyl,
 - h) 7-(imidazo[4.5-b]pyridinyl),
 - i) 4-(3-methylpyridyl).

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- j) 2-pyrimidinyl,
k) 3-pyridazinyl,
l) 2-pyrazinyl,
m) 2-(N-Boc-amino)-4-pyridyl,
5 n) 4-(2-N-acetylamino)-pyridyl,
o) 4-(2-N-benzoylamino-3-methyl)-pyridyl and
p) 4-(2-N-benzoylamino)-pyridyl;

R¹ is: C₁₋₁₅ alkyl;

R² is selected from the group consisting of:

- a) isopropyl,
b) tert-butyl,
c) phenethyl,
15 d) benzyl,
e) 2-amino-2,2-dimethylethyl,
f) 4-aminomethylbenzyl,
g) piperidin-4-yl,
h) piperidin-3-yl,
20 i) pyrrolidin-3-yl,
j) N-methylpiperidin-4-yl,
k) N-benzylpiperidin-4-yl,
l) N-(2-hydroxy-ethyl)piperidin-4-yl,
m) N-methanesulfonylpiperidin-4-yl,
25 n) isobutyl,
o) N-CBz-piperidin-4-yl,
p) N-Bn-piperidin-4-yl,
q) N-Ph-piperidin-4-yl,
r) CH₂-4-(N-Me)-piperidin-4-yl,
30 s) 3-N-Me-piperidinyl,
t) CH₂-morpholin-1-yl. and

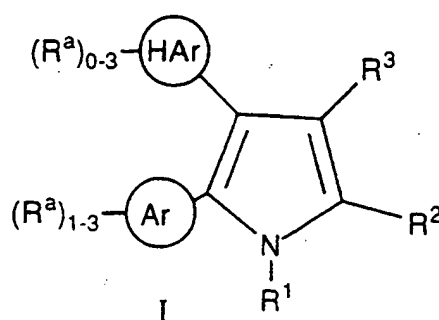
R³ is selected from the group consisting of:

- a) H,
35 b) F,

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- c) Cl,
 d) Br,
 e) CO₂R²⁰,
 f) CONR²⁰R²³ or
 g) CN.

23. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

Ar represents a C₅₋₁₀ aryl, or heteroaryl group, substituted with 1 - 3 groups selected from R^a;

HAr represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 - 3 R^a groups;

each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²⁰, CO₂R²³; CONR²⁰R²³; SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; SO₂NR²⁰CO₂R²¹; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰ and C(NR²⁰)NR²⁰R²³;

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R^1 is selected from the group consisting of: H; C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, aryl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CON(R²⁰)₂, N(R²⁰)C(NR²⁰)NHR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCON(R²⁰)₂, OCONR²⁰SO₂R²¹, C(O)OCH₂OC(O)R²⁰ and OCONR²⁰R²³;

10

R^2 is selected from the group consisting of: C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, and C₂₋₁₅ alkynyl, heterocyclyl, optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from 1-3 of halo, aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, N(R²²)C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²² and OCONR²⁰R²³;

20

R^3 is selected from the group consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, CF₃, NO₂ and heterocyclyl, said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, CN, aryl, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²² and OCONR²⁰R²³;

30

R²⁰ represents a member selected from the group consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

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R^{21} represents a member selected from the group consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, aryl and heteroaryl, optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO_2 or NR^{24} ; said alkyl, alkenyl, alkynyl, aryl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, CN, OR^{20} , $O((CH_2)_nO)_mR^{20}$, $NR^{20}((CH_2)_nO)_mR^{20}$ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR^{20} , $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{22}C(NR^{22})NHR^{22}$, CO_2R^{20} , $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OCONHR^{20}R^{23}$ and $OCON(R^{20})_2$;

R^{22} is selected from the group consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

R^{23} is R^{21} or H;

R^{24} is selected from aryl, COR^{22} , CO_2R^{22} , $CON(R^{20})_2$, R^{23} and SO_2R^{22} ;

n is 1-4;

m is 1-4;

and when two R^{20} groups are present, when R^{20} and R^{21} are present, or when R^{20} and R^{23} are present, said two R^{20} groups, R^{20} and R^{21} or said R^{20} and R^{23} may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a

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heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

24. A compound in accordance with claim 11 wherein:

5 Ar is selected from the group consisting of:

- a) phenyl,
- b) pyridyl,
- c) pyrimidinyl,
- d) thiophenyl,
- 10 e) furanyl,
- f) imidazolyl,
- g) thiazolyl,
- h) isothiazolyl,
- i) oxazolyl and
- 15 j) isoxazolyl;

HAr is selected from the group consisting of:

- a) pyridyl,
- b) quinolyl,
- 20 c) purinyl,
- d) imidazolyl and
- e) imidazopyridine;

R¹ is:

- 25 a) H, or
- b) substituted alkyl;

R² is selected from the group consisting of:

- a) C₁-7-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by : oxo, NR²³,
- 30 b) C₄-7-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by : oxo, NR²³,
- c) C₁-4-alkyl-aminoacyl-C₂-6-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by : oxo, NR²³,

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- d) C₁₋₄-alkyl-aminoacyl-C₄₋₇-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by : oxo, NR²³ or NR²⁴,
e) C₁₋₄-alkyl-aminoacylamino-C₂₋₆-alkyl optionally interrupted by 1 nitrogen atom and optionally substituted by : oxo, NR²³, or
5 f) C₁₋₄-alkyl-aminoacylamino-C₄₋₇-cycloalkyl optionally interrupted by 1 nitrogen atom and optionally substituted by: oxo, NR²³, NR²⁴; wherein the point of attachment to the pyrrole is from the left hand side of the items listed in a through f;

- 10 R³ is: a) H,
b) alkyl,
c) halo,
d) CO₂R²⁰.

- 15 25. A compound according to claim 11 wherein:

Ar is selected from the group consisting of:

- a) phenyl,
b) 4-fluorophenyl,
c) 4-chlorophenyl,
20 d) 3-fluorophenyl,
e) 3-chlorophenyl,
f) thiophen-2-yl,
g) thiophen-3-yl,
h) 4-fluorothiophen-2-yl,
25 i) 4-fluorothiophen-3-yl,
j) 5-fluorothiophen-2-yl,
k) 5-fluorothiophen-3-yl,
l) 4-chlorothiophen-2-yl,
m) 4-chlorothiophen-3-yl,
30 n) 5-chlorothiophen-2-yl,
o) 5-chlorothiophen-3-yl,
p) 3-methylphenyl,
q) 3,4-dichlorophenyl, and
r) 3-hydroxyphenyl;

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HAr is selected from the group consisting of:

- 5
- a) 4-pyridyl,
 - b) 4-(2-methylpyridyl),
 - c) 4-(2-aminopyridyl),
 - d) 4-(2-methoxypyridyl),
 - e) 4-quinolyl,
 - f) 4-pyrimidinyl,
 - 10 g) 9-purinyl,
 - h) 7-(imidazo[4.5-b]pyridinyl), and
 - i) 4-(3-methylpyridyl);

R¹ is: H;

15 R² is selected from the group consisting of:

- a) isopropyl,
- b) tert-butyl,
- c) phenethyl,
- d) benzyl,
- 20 e) 2-amino-2,2-dimethylethyl,
- f) 4-aminomethylbenzyl,
- g) glycylaminomethyl,
- h) (L)-alanylaminomethyl,
- i) 2-amino-2,2-dimethylacetylaminomethyl,
- 25 j) N,N-dimethylaminoethyl-N-methylaminocarbonylaminomethyl,
- k) 3-piperidinecarbonylaminomethyl,
- l) 4-piperidinecarbonylaminomethyl,
- m) piperidine-4-yl,
- 30 n) piperidine-3-yl,
- o) pyrrolidin-3-yl,
- p) N-methylpiperidine-4-yl,
- q) N-benzylpiperidine-4-yl,
- r) N-(2-hydroxyethyl)piperidine-4-yl and

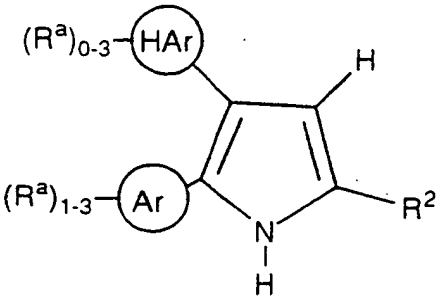
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s) N-methanesulfonylpiperidine-4-yl; and

R³ is selected from the group consisting of:

- 5 a) H,
 b) F,
 c) Cl and
 d) Br.

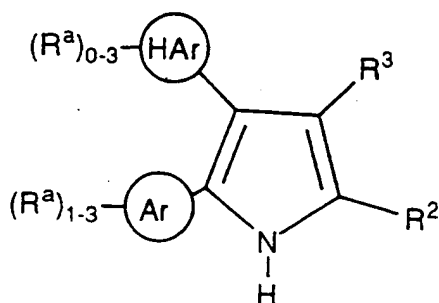
26. A compound according to claim 1 falling within one of the
 10 following tables:

TABLE I			
			
	R ²	(R ^a) ₁₋₃ -Ar	(R ^a) ₀₋₃ -HAr
	t-butyl	Ph-4-F	3-methyl-4-pyridyl
	t-butyl	Ph-4-F	4-quinolinyl
	t-butyl	Ph-4-F	2-methyl-4-pyridyl
	N-Bn-piperidin-4-yl	Ph-4-F	4-pyridyl
	N-Ph-piperidin-4-yl	Ph-4-F	4-pyridyl
	N-Me-piperidin-4-yl	Ph-4-Cl	4-pyridyl
	N-Me-piperidin-4-yl	Ph-3,4-di-F	4-pyridyl

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	N-Me-piperidin-4-yl	Ph-3-Cl	4-pyridyl
	t-butyl	Ph-2-OMe	4-pyridyl
	t-butyl	Ph-3-OMe	4-pyridyl
	t-butyl	Ph-4-OMe	4-pyridyl
	t-butyl	Ph-4-Cl	4-pyridyl
	t-butyl	Ph-3-Cl	4-pyridyl
	t-butyl	Ph-3,4-di-F	4-pyridyl
	t-butyl	Ph-3,4-di-Cl	4-pyridyl
	t-butyl	Ph-3-CF ₃	4-pyridyl
	t-butyl	Ph-4-SMe	4-pyridyl
	t-butyl	Ph-4-S(O)Me	4-pyridyl
	4-piperidinyl	Ph-4-F	4-pyridyl
	N-Me-piperidin-3-yl	Ph-4-F	4-pyridyl
	t-butyl	Ph-4-NO ₂	4-pyridyl
	t-butyl	Ph-4-NMe ₂	4-pyridyl
	t-butyl	Ph-2-Cl	4-pyridyl
	N-Me-piperidin-4-yl	Ph-3-CF ₃	4-quinolinyl
	4-piperidinyl	Ph-3-CF ₃	4-quinolinyl
	N-CBz-piperidin-4-yl	Ph-2-CF ₃	4-(2-F)-pyridyl
	N-methylpiperidin-4-yl	Ph-4-F	2-methylpyridin-4-yl
	N-methylpiperidin-4-yl	Ph-3-CF ₃	2-methylpyridin-4-yl
Me = methyl, CBz = benzyloxycarbonyl Bn = benzyl Ph = phenyl Boc = butoxycarbonyl			

TABLE II

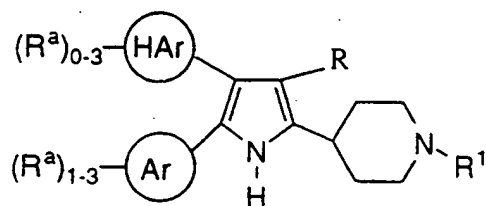


	R ²	(R ^a) ₁₋₃ -Ar	(R ^a) ₀₋₃ -HAr	R ³
	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CN
	t-butyl	Ph-4-F	2-methyl-4-pyridyl	COMe
	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CONHMe
	t-butyl	Ph-4-F	2-methyl-4-pyridyl	SO ₂ Et
	t-butyl	Ph-4-F	2-methyl-4-pyridyl	COOEt
	t-butyl	Ph-4-F	4-quinoliny	CN
	t-butyl	Ph-4-F	2-quinoliny	CN
	t-butyl	Ph-4-F	2-pyrimidiny	CN
	t-butyl	Ph-4-F	4-pyrimidiny	CN
	t-butyl	Ph-4-F	3-pyridaziny	CN
	t-butyl	Ph-4-F	2-pyraziny	CN
	t-butyl	Ph-4-F	2-pyrimidiny	CN
	t-butyl	Ph-4-F	4-pyrimidiny	CN
	t-butyl	Ph-4-F	2-imidazo-(4,5-b)-pyridiny	CN
	t-butyl	Ph-4-F	4-(2-amino)-pyridyl	CN
	t-butyl	Ph-4-F	4-(2-N-benzyl-amino)-pyridyl	CN
	t-butyl	Ph-4-F	4-(2-acetylamino)-pyridyl	COMe
	t-butyl	Ph-4-F	4-pyridyl	CN
	t-butyl	Ph-4-F	4-pyridyl	CONH-iBu
	t-butyl	Ph-4-F	4-pyridyl	COMe
	i-butyl	Ph-4-F	4-pyridyl	CN
	N-Me-piperidin-4-yl	Ph-4-F	4-pyridyl	COMe
	N-Bn-piperidin-4-yl	Ph-4-F	4-pyridyl	COMe
	N-Ph-piperidin-4-yl	Ph-4-F	4-pyridyl	COMe
	CH ₂ -4-(N-Me)-piperaziny	Ph-4-F	4-pyridyl	CN
	N-Me-piperidin-4-yl	Ph-4-F	4-pyridyl	CN

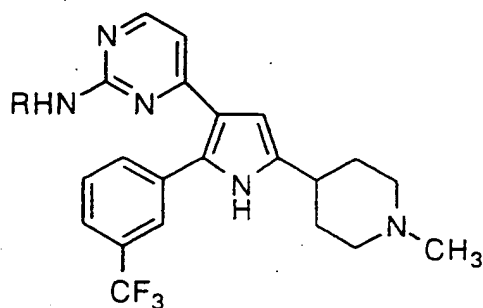
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	N-Me-piperidin-4-yl	Ph-4-Cl	4-pyridyl	CN
	t-butyl	Ph-2-OMe	4-pyridyl	CN
	t-butyl	Ph-3-OMe	4-pyridyl	CN
	t-butyl	Ph-4-OMe	4-pyridyl	CN
	t-butyl	4-(4-(N-COCH ₃)-piperazinyl)-Ph	4-pyridyl	CN
	t-butyl	4-(morpholinyl)-Ph	4-pyridyl	CN
	t-butyl	Ph-4-Cl	4-pyridyl	CN
	t-butyl	Ph-3-Cl	4-pyridyl	CN
	t-butyl	Ph-3,4-di-Cl	4-pyridyl	CN
	t-butyl	Ph-3-CF ₃	4-pyridyl	CN
	t-butyl	Ph-4-S-Me	4-pyridyl	CN
	t-butyl	Ph-4-S(O)-Me	4-pyridyl	CN
	4-piperidinyl	Ph-4-F	4-pyridyl	CN
	3-N-Me-piperidinyl	Ph-4-F	4-pyridyl	CN
	CH ₂ -morpholin-1-yl	Ph-4-F	4-pyridyl	CN
	t-butyl	Ph-4-NO ₂	4-pyridyl	CN
	t-butyl	Ph-4-NMe ₂	4-pyridyl	CN
	t-butyl	Ph-2-Cl	4-pyridyl	CN
	4-piperidinyl	Ph-4-F	4-pyridyl	CN
	t-butyl	Ph-4-F	2-pyridyl	CN
	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CN
	t-butyl	Ph-4-F	3-methyl-4-pyridyl	CN
	cyclohexyl	Ph-4-F	4-pyridyl	CN
	i-propyl	Ph-4-F	4-pyridyl	CN
	1-cyclopropyl-ethyl	Ph-4-F	4-pyridyl	CN
	t-butyl	Ph-4-F	2,4-dimethylpyridin-4-yl	CN
	4-(N-Cbz)-piperidinyl	Ph-4-F	4-pyridyl	H
	4-(N-Cbz)-piperidinyl	Ph-4-F	4-quinolinyl	H
	4-(N-Cbz)-piperidinyl	3-(CF ₃)-Ph	4-(2-F)-pyridyl	
	t-butyl	Ph-4-F	2,6-dimethylpyridyl	CN

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	$(R^a)_{1-3}-Ar$	$(R^a)_{0-3}-HAr$	R	R ¹		
	3,4-di-F-C ₆ H ₃	4-C ₅ H ₄ N	CH ₃	CH ₃		
	3-CF ₃ -C ₆ H ₄	4-C ₅ H ₄ N	Ethyl	CH ₃		
	3-CF ₃ -C ₆ H ₄	4-C ₅ H ₄ N	CH ₃	CH ₃		
	3-CF ₃ -C ₆ H ₄	4-C ₅ H ₄ N	CH ₃	H		
	3-CF ₃ -C ₆ H ₄	4-C ₅ H ₄ N	CH ₃	SO ₂ C ₆ H ₅		

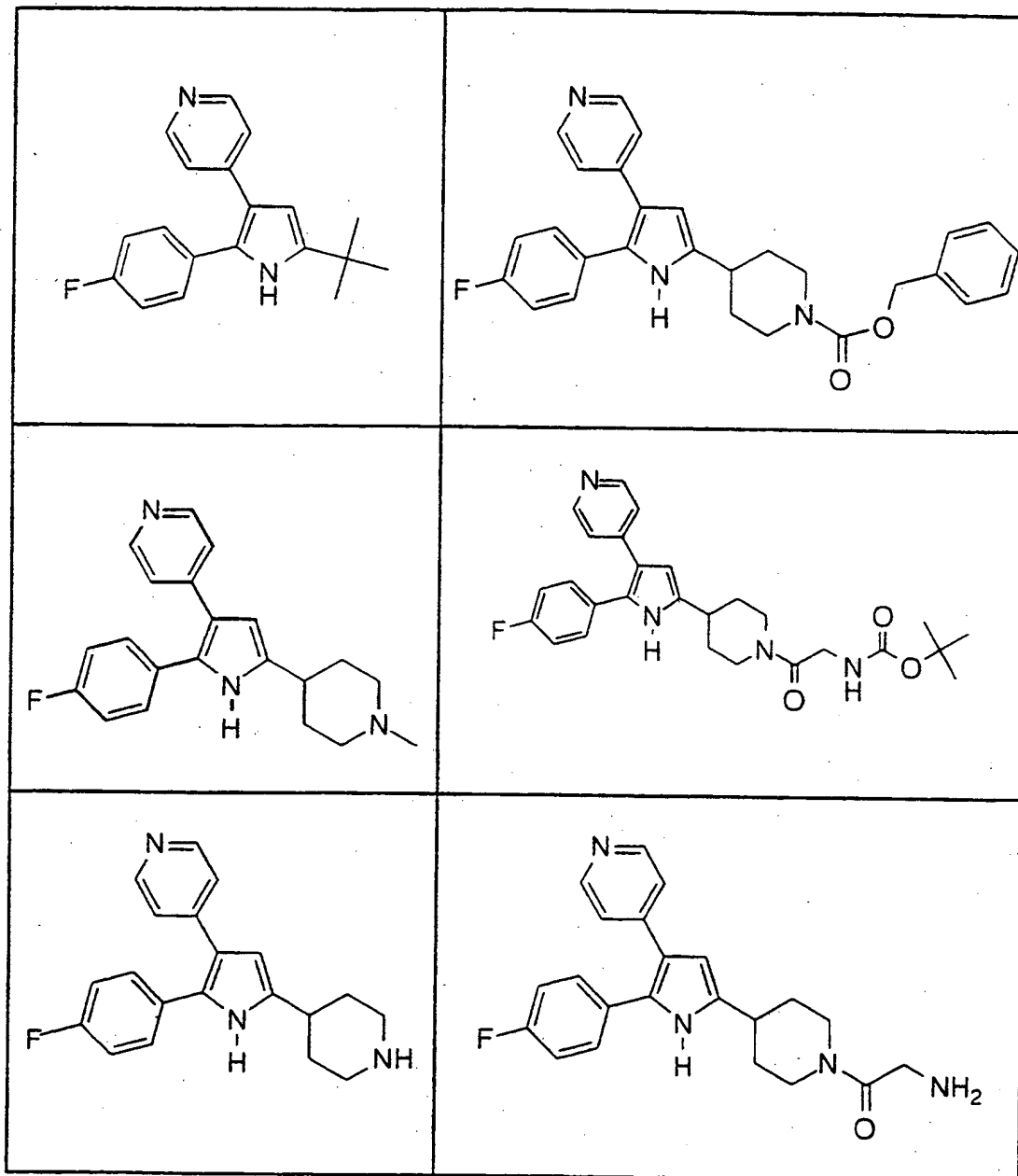


	R	
	cyclopropyl	
	methyl	
	phenethyl	
	s-α-Me-benzyl	

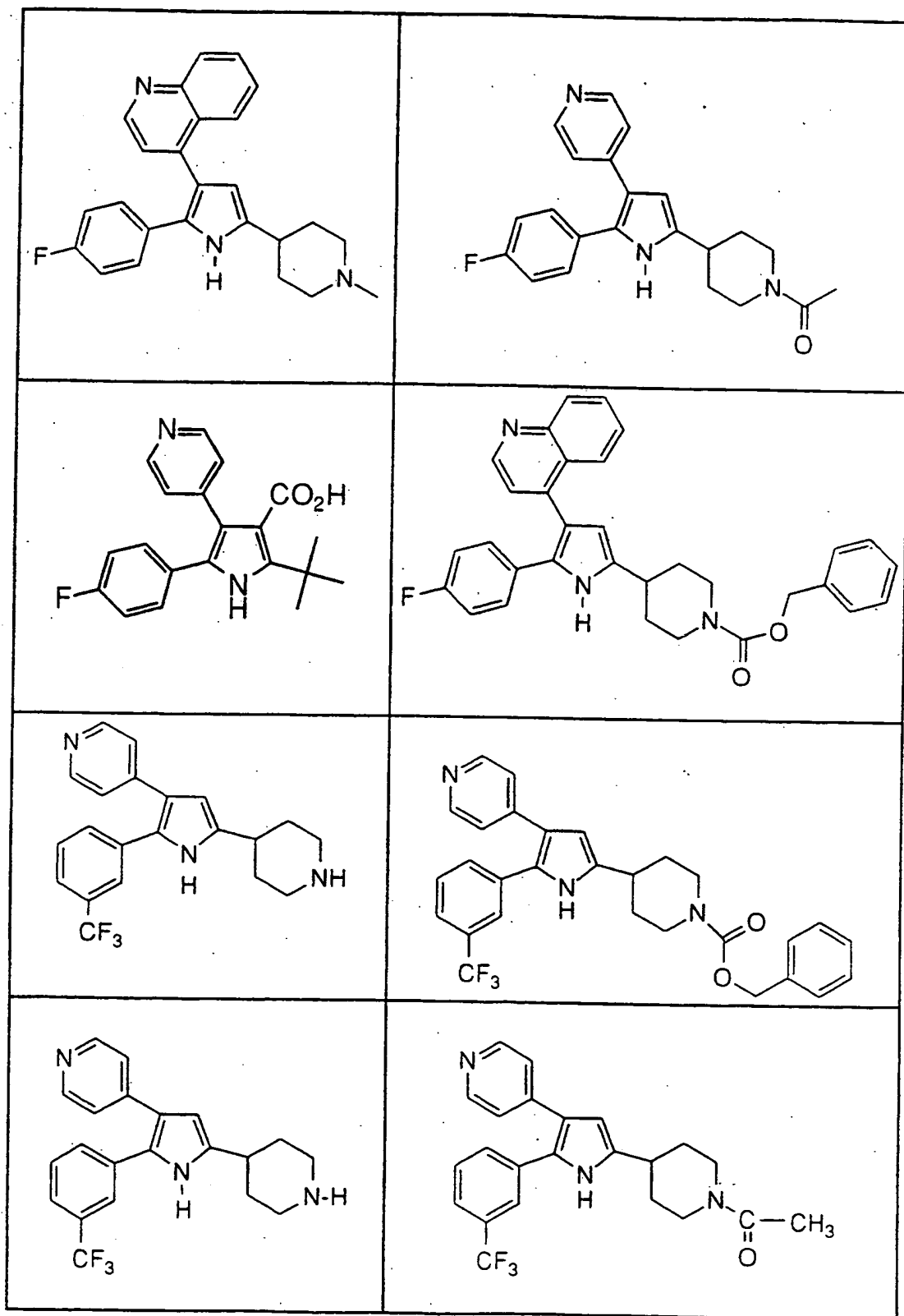
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27. A compound in accordance with claim 1 represented by one of the following structural formulas:

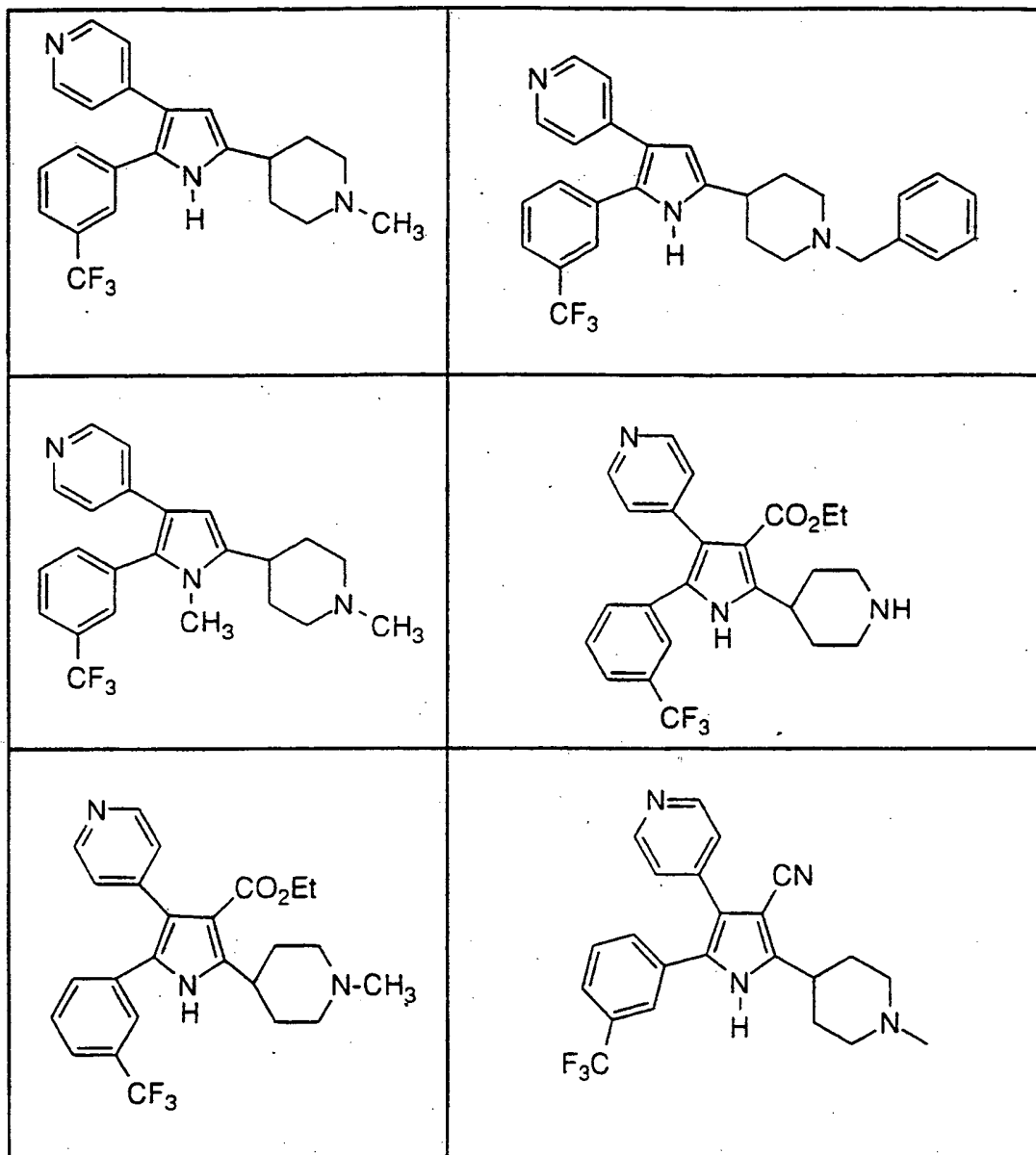
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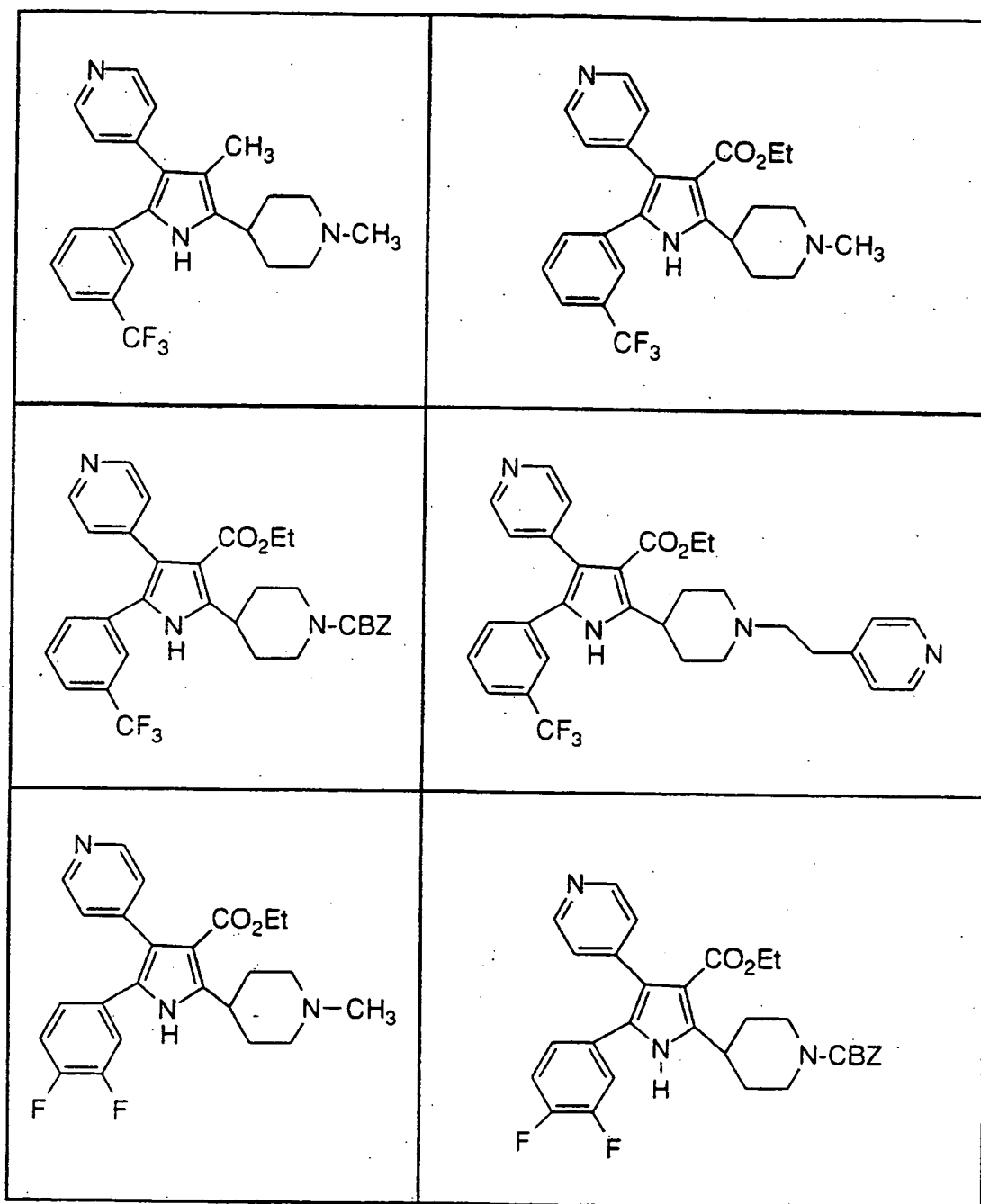
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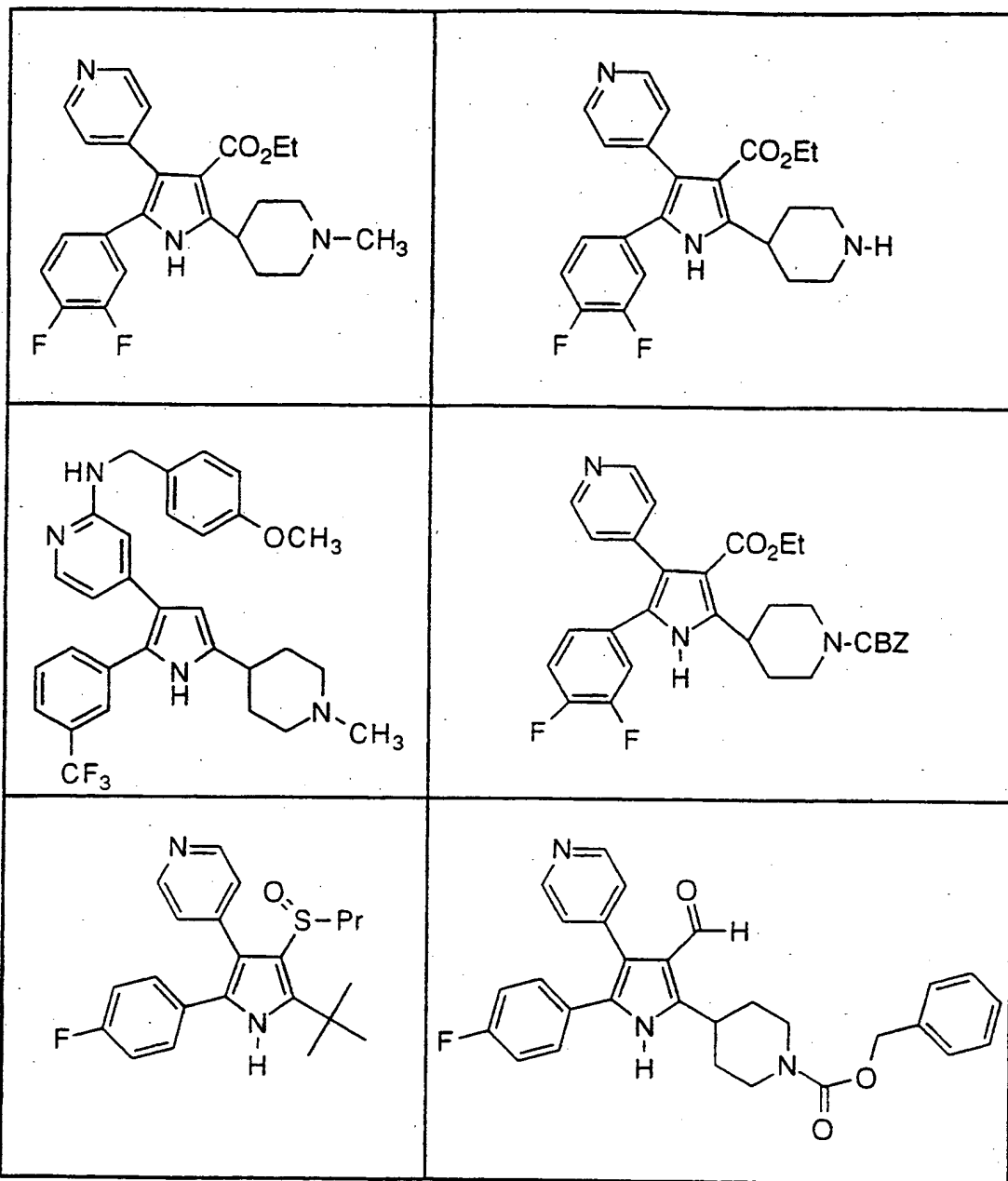
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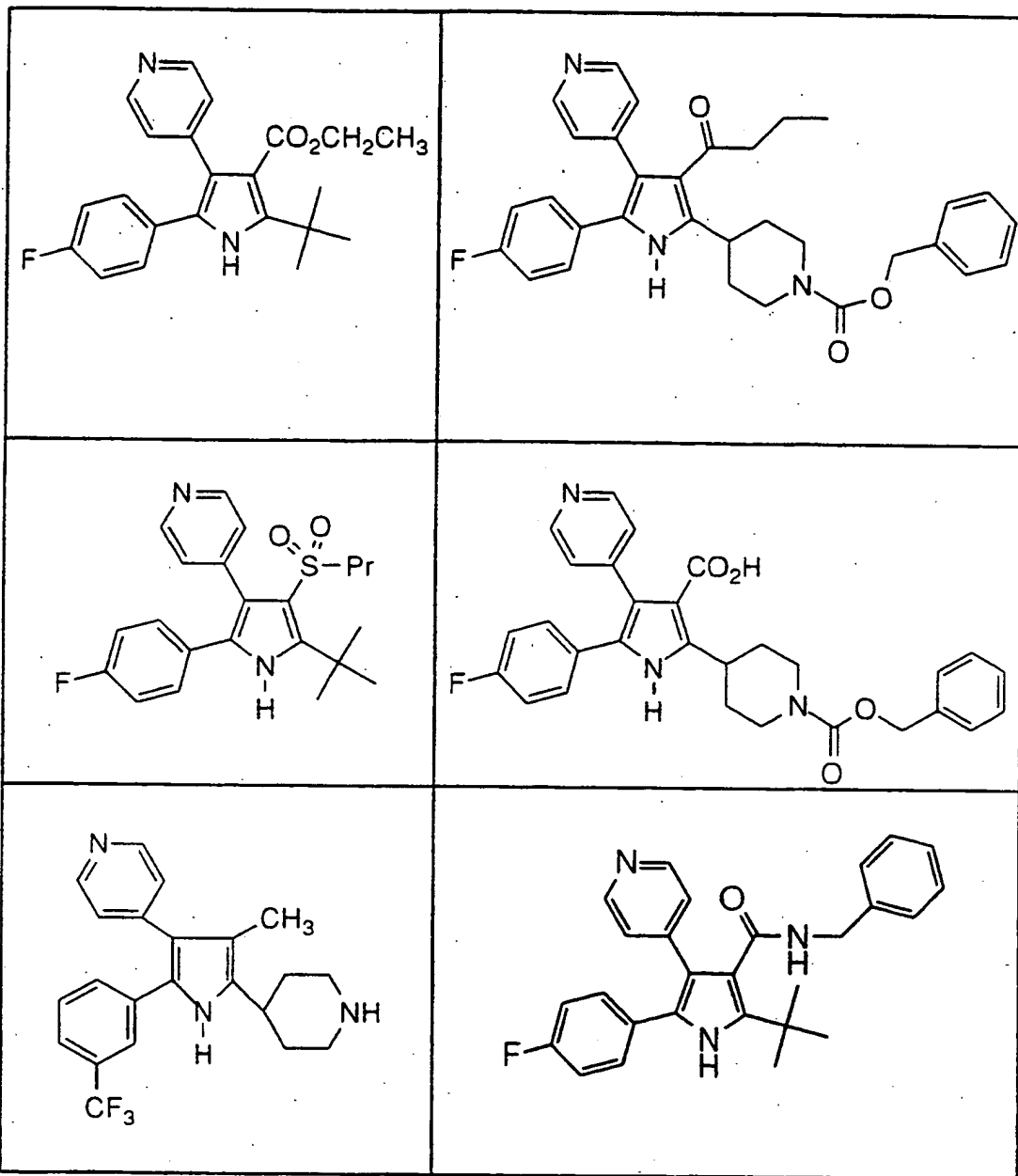
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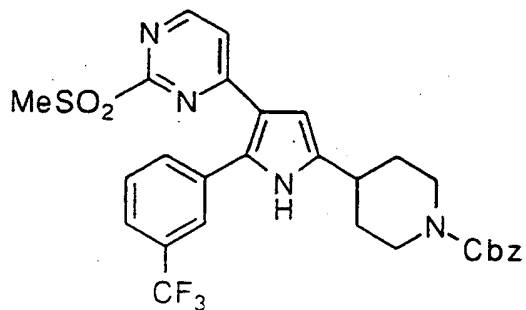
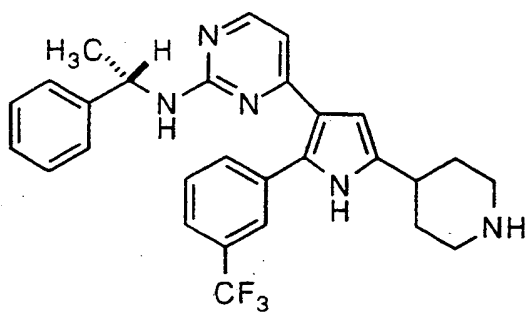
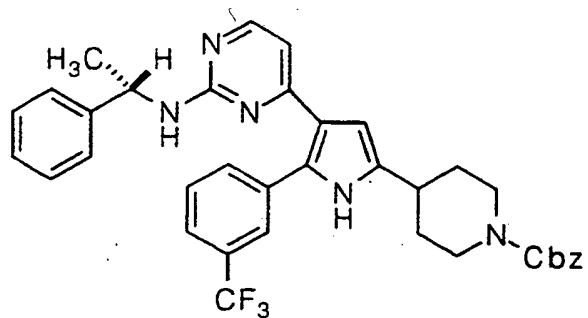
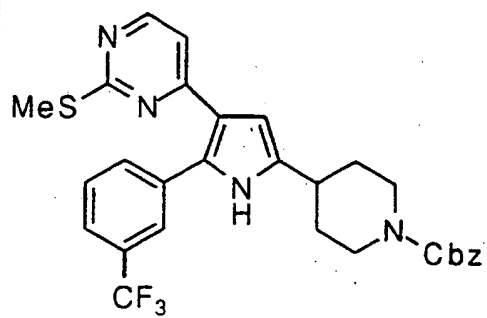
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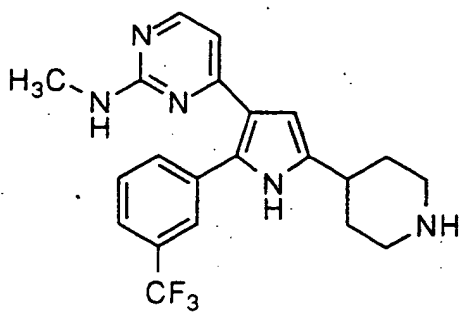
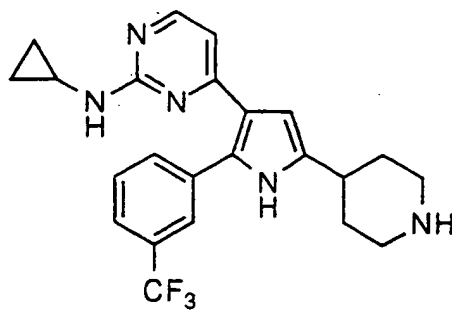
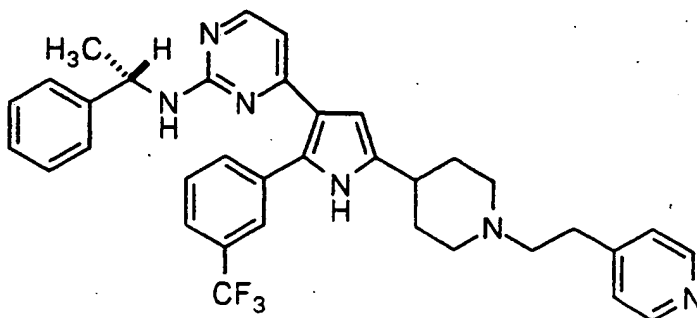
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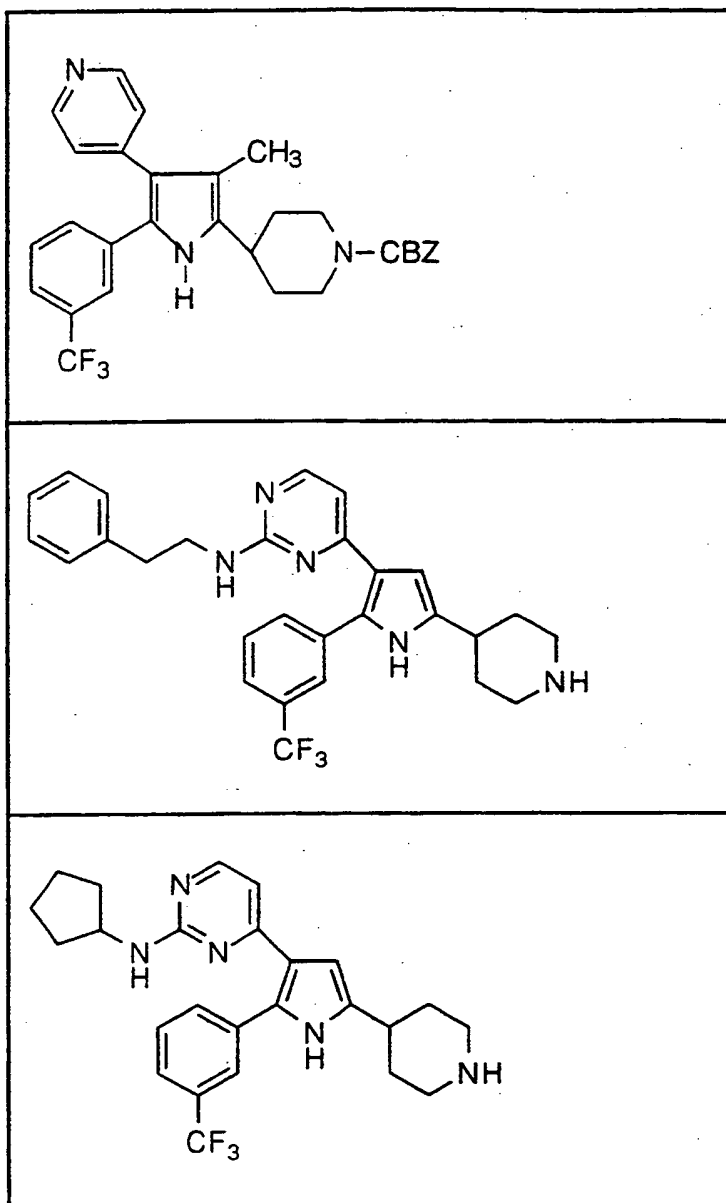
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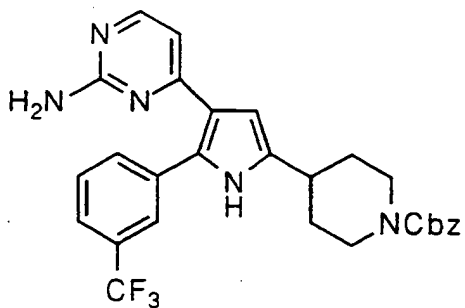
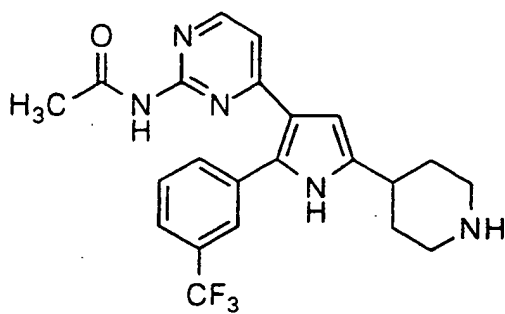
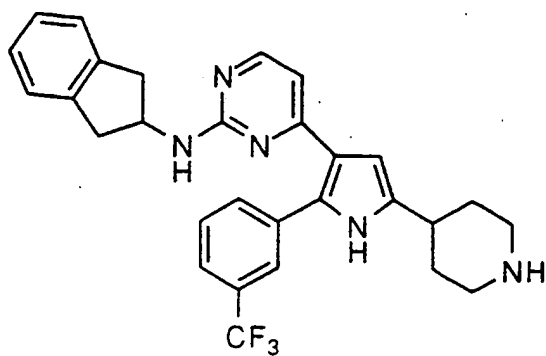
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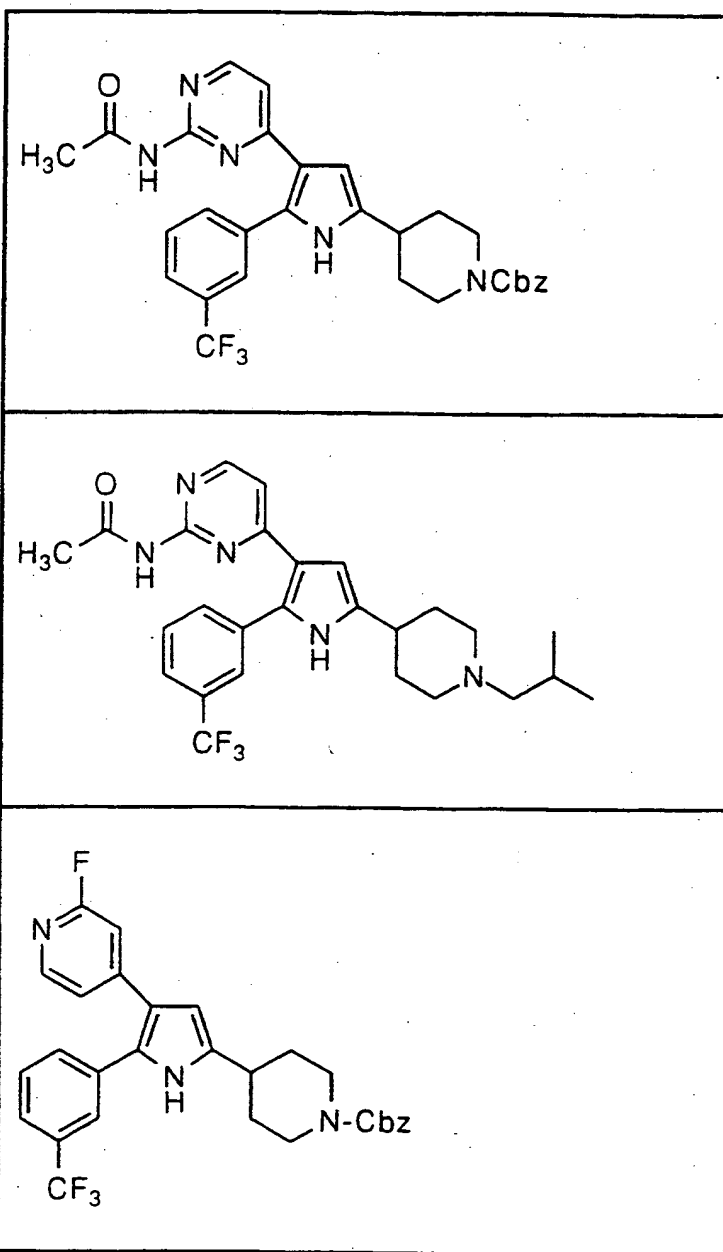
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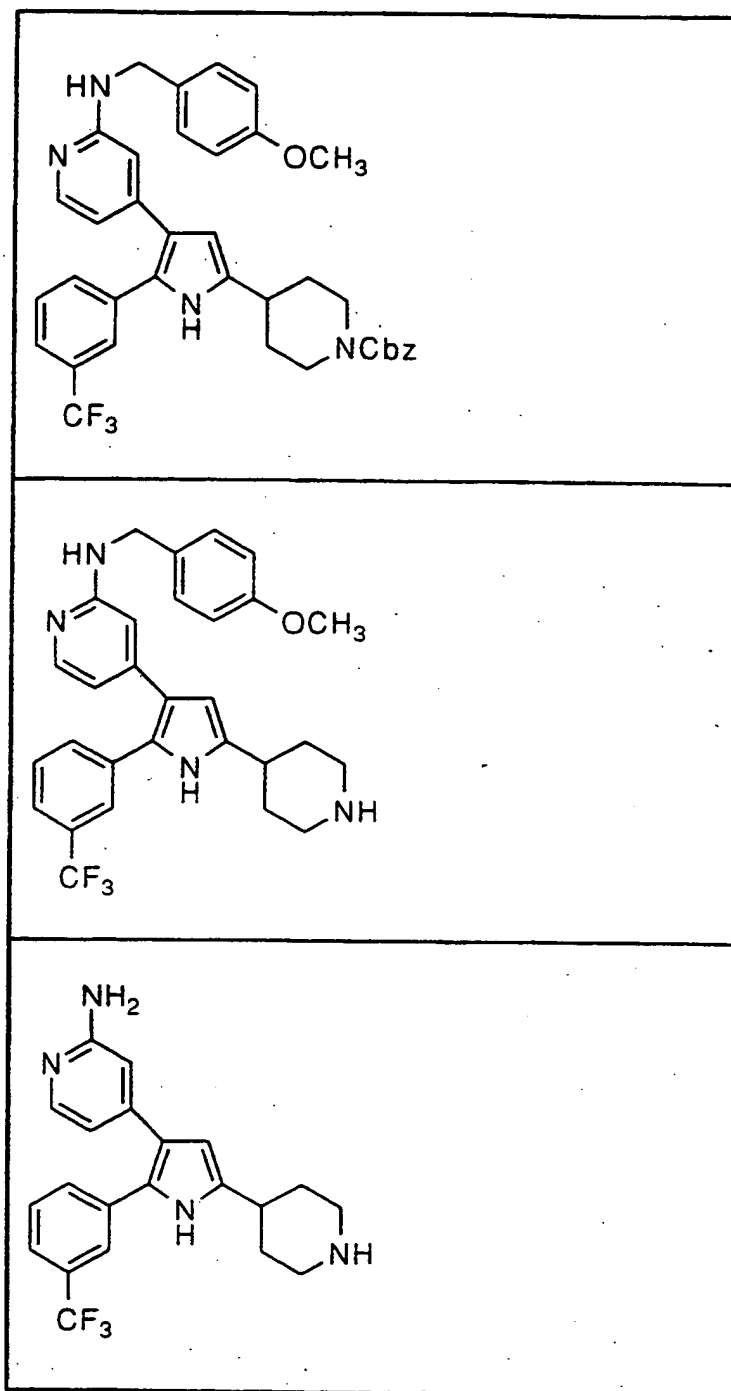
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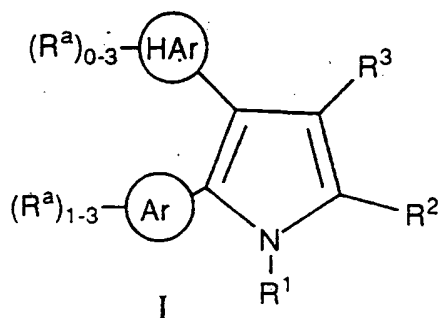


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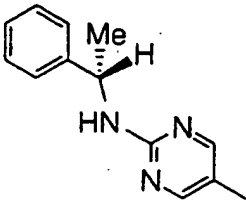
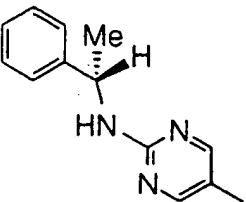
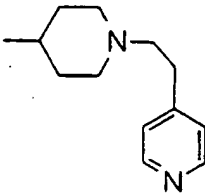
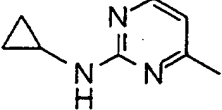
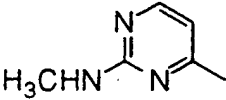
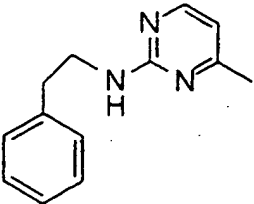
28. A compound in accordance with claim 1 falling within the following table:

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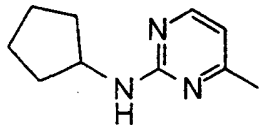
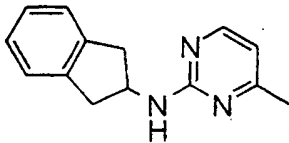
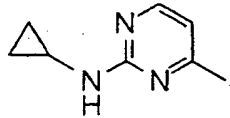
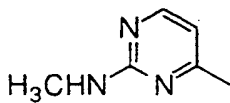
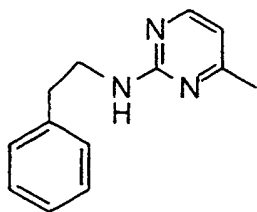
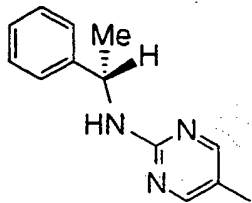


R ¹	(R ^a) ₁₋₃ -Ar	(R ^a) ₀₋₃ -HAr	R ³	R ²
H	4-F-Ph	4-pyridyl	H	t-Bu
H	4-F-Ph	4-pyridyl	H	4-(N-Cbz)-piperidinyl
H	4-F-Ph	4-pyridyl	H	4-(N-Me)-piperidinyl
H	4-F-Ph	4-quinoliny	H	4-(N-Cbz)-piperidinyl
H	4-F-Ph	4-pyridyl	H	4-piperidinyl
H	4-F-Ph	4-quinoliny	H	4-(N-Me)-piperidinyl
H	4-F-Ph	4-pyridyl	H	4-(N-COCH ₂ NH ₂)-piperidinyl
H	4-F-Ph	4-pyridyl	H	4-(N-COCH ₃)-piperidinyl
H	4-F-Ph	4-pyridyl	H	4-(N-COCH ₂ NH-CO ₂ tBu)piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-CBz)-piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	H	4-piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-Me)-piperidinyl
H	3-(CF ₃)-Ph	4-(2-F)-pyridyl	H	4-(N-CBz)-piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-CBz)-piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	Me	4-[N-SO ₂ Ph]-piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-acetyl)-piperidinyl
H	3,4-di-F-Ph	4-pyridyl	Et	4-(N-Me)-piperidinyl
H	3,4-di-F-Ph	4-pyridyl	Me	4-(N-Me)-piperidinyl
H	3,4-di-F-Ph	4-pyridyl	-CO ₂ Et	4-(N-Me)-piperidinyl
H	3-(CF ₃)-Ph	4-pyridyl	-CO ₂ Et	4-(N-Me)-piperidinyl

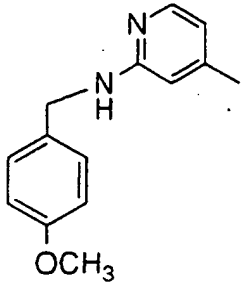
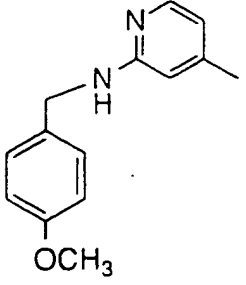
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H	3-(CF ₃)-Ph	4-pyridyl	CH ₃	4-(N-Me)-piperidiny
H	3-(CF ₃)-Ph	4-pyridyl	CH ₃	4-piperidiny
H	3-(CF ₃)-Ph		H	4-piperidiny
H	3-(CF ₃)-Ph		H	
H	3-(CF ₃)-Ph		H	4-piperidiny
H	3-(CF ₃)-Ph		H	4-piperidiny
H	3-(CF ₃)-Ph		H	4-piperidiny

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H	3-(CF ₃)-Ph		H	4-piperidinyl
H	3-(CF ₃)-Ph		H	4-piperidinyl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl
H	3-(CF ₃)-Ph		H	N-methyl-piperidin-4-yl

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H	3-(CF ₃)-Ph		H	4-piperidinyll
H	3-(CF ₃)-Ph		H	4-(N-Me)-piperidinyll
H	3-(CF ₃)-Ph	4-pyridyl	-CO ₂ Et	4-piperidinyll
H	3-(CF ₃)-Ph	4-pyridyl	-CO ₂ Et	N-(2-ethylpyridin-4-yl)piperidin-4-yl
H	3,4-di-F-phenyl	4-pyridyl	-CO ₂ Et	4-piperidinyll
CH ₃	3-(CF ₃)-Ph	4-pyridyl	H	4-(N-Me)-piperidinyll

29. A method of treating a cytokine mediated disease in a mammal in need of such treatment, which comprises administering to said mammal an anti-cytokine effective amount of a compound of claim 1.

30. The method according to claim 29 wherein the cytokine inhibited is IL-1.

31. The method according to claim 29 wherein the cytokine inhibited is TNF.

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32. The method according to claim 29 wherein the cytokine inhibited is IL-8.

5 33. The method according to claim 29 wherein the cytokine inhibited is IL-6.

34. The method according to claim 29 wherein the cytokine mediated disease is septic shock, endotoxic shock, gram negative sepsis or toxic shock syndrome.

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35. The method according to claim 29 wherein the cytokine mediated disease is bone resorption diseases, graft versus host reaction, atherosclerosis, arthritis, osteoarthritis, rheumatoid arthritis, gout, psoriasis or topical inflammatory disease states.

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36. The method according to claim 29 wherein the cytokine mediated disease is adult respiratory distress syndrome, asthma or chronic pulmonary inflammatory disease.

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37. The method according to claim 29 wherein the cytokine mediated disease is cardiac or renal reperfusion injury, thrombosis or glomerulonephritis.

25 38. The method according to claim 29 wherein the cytokine mediated disease is Crohn's disease, ulcerative colitis or inflammatory bowel disease.

39. The method according to claim 29 wherein the cytokine mediated disease is cachexia.

30

40. The method according to claim 29 wherein the cytokine mediated disease is a viral infection.

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41. A method of treating inflammation mediated by excess production of prostaglandins in a human in need of such treatment, which comprises administering to said human an effective cytokine interfering amount of a compound of claim 1.

5

42. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

10

43. A pharmaceutical composition made by combining an effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12917

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KONAKAHARA et al. One-pot synthesis of pyrroles from N-silyl-1-azaallyl anions. Heterocycles. 01 May 1993, Vol. 35, No. 2, pages 1171-1184, see entire document.	1-25
A, P	WO 96/17841 A1 (NIPPON SODA CO., LTD.) 13 June 1996 (13.06.96), see the entire document.	1-28
A	EP 0 300 688 A1 (FISON PLC) 25 January 1989 (25.01.89), see the entire document.	1-43



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 OCTOBER 1996

Date of mailing of the international search report

28 OCT 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

RICHARD S. MYERS, JR.

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/12917

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/44, 31/50, 31/445, 31/495, 31/505, 31/535; C07D 211/68, 211/80, 213/02, 239/02, 401/00, 401/04, 471/02, 473/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/235.5, 252, 253, 256, 303, 274, 275, 314, 318, 341, 343; 544/120, 238, 272.7, 318, 331, 332, 333, 363, 364, 405; 546/119, 167, 194, 208, 276.4

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/235.5, 252, 253, 256, 303, 274, 275, 314, 318, 341, 343; 544/120, 238, 272.7, 318, 331, 332, 333, 363, 364, 405; 546/119, 167, 194, 208, 276.4

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